CRS Report for Congress

Environmental Tobacco Smoke and Lung Cancer Risk

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November 14, 1995

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OVERVIEW

GENERAL ISSUES

In response to requests from Congress, this report presents an analysis of the potential health effects of environmental tobacco smoke (ETS). The report concentrates on possible lung cancer risk because of the availability of published literature and resource constraints within CRS. A brief overview of ETS and the risk of heart disease and childhood respiratory illness is also presented.

A substantial body of evidence built up over the last 40 years indicates that smoking is a major cause of illness and premature death. In recent years, several reports have also concluded that exposure to environmental tobacco smoke (ETS) can cause lung cancer in people who have never smoked. In 1992, the Environmental Protection Agency (EPA) classified ETS as a known human carcinogen and estimated that ETS exposure is responsible for about 3000 lung cancer deaths each year among adult nonsmokers. EPA's findings have received much support from the scientific community, but have been criticized by other scientists, statisticians and the tobacco industry.

Environmental tobacco smoke is a highly diluted combination of mainstream smoke exhaled by smokers and sidestream smoke released directly from the burning tips of cigarettes. Researchers have concluded that ETS contains most, if not all, of the carcinogenic and toxic compounds that are present in mainstream smoke. Studies that measured cotinine — a nicotine derivative — levels in blood and urine indicate that there is widespread exposure to ETS, and measurable uptake of ETS by nonsmokers. According to the EPA, the chemical similarities between mainstream smoke and ETS, and the evidence of exposure to, and uptake of, ETS among nonsmokers is sufficient to conclude that ETS is a lung-cancer hazard.

The EPA based its estimate of the magnitude of the ETS lung cancer risk among nonsmokers on an analysis of over 30 epidemiologic studies of lung cancer among adult non-smoking women. These studies relied on spousal smoking as a surrogate for ETS exposure and classified the women as exposed or unexposed on the basis of whether their husbands smoked. The lung cancer risk among the exposed women was compared to that of the unexposed women.

Since the EPA report was issued, the largest and most recent case-control epidemiologic study included in the EPA findings has been completed, and three other large, case-control studies have been published. Two of these studies[1] show no increased average risk, one[2] shows a statistically significant increased

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[1] Kabat, G.l., et.al., *American Journal of Epidemiology*, Vol.142, No.2, 1995, p.141-148; Brownson,R.C., et.al., *American Journal of Public Health*, Vol.82, No.11, 1992, p.1525-1530.

[2] Fontham, E.T.H., et.al.,*Journal of the American Medical Association*, Vol.271,No.22, 1994, p.1752-1759.

average risk while the fourth[3] shows an increased average risk which is not statistically significant at the 95 percent level.

An extensive review of the literature on ETS and lung cancer risk indicates that any lung cancer risk appears to increase as integrated (time and quantity) exposure to ETS increases. Three of the four recent studies (Fontham, et.al., Brownson, et.al., and Stockwell, et.al.) report statistically significant excess risk values at the highest exposure levels (measured in pack-years [packs per day times years exposed] in two cases and in smoker years in another), and about one-third of the studies reviewed by EPA for dose response behavior show a statistically significant (at the 95 percent level) upward trend. While there is evidence of an upward dose reponse trend, the results are not definitive. And even at the greatest integrated exposure levels, the measured risks are still subject to uncertainty.

Calculations based on data from the Fontham, et.al., study and assuming an average exposure for the entire population at risk (a no-threshold model) result in a range of 470 to 5500 annual lung cancer deaths in the U.S. from ETS with a mean value of 2780. This compares to a mean value of 3300 calculated by EPA under the same assumption. Data from the Brownson, et.al, study, on the other hand, produce no annual lung cancer deaths from ETS also under the no-threshold assumption. If a threshold model is used to simulate the upper limit of a possible upward dose response behavior, the mean number of lung cancer deaths is 440 calculated from the Fontham, et.al, data and 530 for the Brownson, et.al., data. Over 70 percent of these deaths calculated in the no-threshold example and all those calculated in the threshold model occur to individuals who are exposed to both spousal and background ETS. The remaining deaths in the no-threshold model would result from exposure only to background ETS.

The threshold model results are consequences of the model chosen. It is possible that there may be some exposed to sufficient background ETS to be over the threshold without spousal ETS. An effect like this, however, may be very difficult to detect without very large samples.

Using the results obtained from the Fontham, et.al., data in the no-threshold example, a person exposed to spousal and background ETS has about a 2/10 of one percent chance of dying of lung cancer from the ETS over her lifetime. For a person exposed only to background ETS, the number drops to about 7/100 of one percent.

SOURCES OF UNCERTAINTY

The major sources of uncertainty for interpreting the epi results are confounders -- factors other than ETS which could explain the measured risk values, and misclassification. The latter includes identifying current smokers or

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[3] Stockwell, H.G.,et.al.,*Journal of the National Cancer Institute*, Vol.84,No.18, 1992, p.1417-1422.

recently quit smokers as never smokers (smoker misclassification), identifying a person as exposed to ETS because her spouse smoked when in reality she was not subject to any exposure (exposure misclassification), and under or over estimating the amount of ETS exposure (recall bias).

Evidence from a number of studies examining possible confounders appears inconclusive about whether they may be responsible for the risk values measured in the ETS studies. The statistical uncertainties exhibited in the epi studies of most of these possible confounders suggests that none can be considered a clear cause or inhibitor of lung cancer. Furthermore, there is mixed evidence about the correlation of these confounders with increasing integrated exposure to ETS. The number of studies on confounders is not large, however, and it is possible that other confounders exist which have not been identified. Additional research appears to be important.

There are several types of misclassification errors that could occur in these epi studies. Some of them, such as exposure misclassification, would result in measured relative risk values below the actual values, while others, including smoker misclassification and recall bias would result in the measured risk values being overstated. For the Fontham, et.al., and Brownson, et.al., data, smoker misclassification rates of less than 10 percent would account for all of the measured risk at the highest exposure levels in those studies. An even smaller rate -- less than 3 percent -- would cause those risk values to be no longer statistically significant at the 95 percent level. While accounting for exposure misclassification will raise the measured risk values, simulated calculations using the Fontham, et.al., data indicate that misclassification rates greater than 20 percent would be necessary to increase risk values by as much as 5 percent. Recall bias simulations on the same data indicate that overestimating exposure by 10 to 20 percent would result in a reduction of measured risk by about 20 percent at the higher exposure levels.

Information on misclassification rates is skimpy at best. For the exposure and recall categories, it is virtually non-existent. Nevertheless, these simulated calculations indicate that misclassification can be a potent uncertainty in these ETS epi studies, and could account for the measured risk values. Further research on this issue appears called for.

OCCUPATIONAL RISK

The Occupational Safety and Health Administration (OSHA) assessed the lung cancer risk from workplace exposure to ETS as part of its proposed indoor air quality rule. The agency may choose to make substantial revisions to the ETS risk assessment before releasing a final regulation. Independent scientists and tobacco industry researchers and consultants have submitted new data and analyses to the agency for possible inclusion in a revised risk assessment.

Although there are no specific occupational epi studies, several residential studies also collected data on workplace ETS exposure and reported estimates of occupational lung cancer risk. OSHA based its risk assessment on a

workplace risk estimate by Fontham et al., which indicated an increased risk, and chose not to use the remaining estimates which found no overall association between workplace exposure and lung cancer. Moreover, it assumed that workplace exposure is comparable to residential exposure, though studies that measured cotinine levels in nonsmokers suggest that residential and other non-workplace exposure may be more important that workplace exposure. If, on average, workplace ETS exposure is lower than residential exposure, then it is likely that relatively few workers would be exposed to sufficient ETS to be at increased risk for lung cancer. More extensive workplace exposure data are required before this issue can be resolved.

INTRODUCTION

The health effects of cigarette smoking have been the subject of intensive scientific investigation since the 1950s. Smoking is linked to leading causes of chronic illness and premature death, including lung cancer and other malignancies, heart disease and stroke, and chronic obstructive pulmonary disease (e.g., bronchitis and emphysema). The Public Health Service estimates that smoking accounts for 87 percent of all lung cancer deaths, 82 percent of all deaths from chronic obstructive pulmonary disease, and 21 percent of all coronary heart disease deaths.

More recently, there has been concern that nonsmokers may be at risk when exposed to environmental tobacco smoke (ETS) that occurs in indoor environments occupied by smokers. Researchers often refer to the involuntary inhalation of ETS by nonsmokers as passive smoking. In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service both released reports on the health effects of passive smoking.[4] Both reports concluded that ETS can cause lung cancer in adult nonsmokers. That same year, a report by the International Agency for Research on Cancer (IARC) concluded that passive smoking gives rise to some risk of cancer, based on considerations related to biological plausibility.[5]

A recent review of the health effects of passive smoking in the workplace conducted by the National Institute for Occupational Safety and Health determined that "the collective weight of evidence" indicates that ETS poses an increased risk of lung cancer and possibly heart disease in occupationally exposed workers.[6] An extensive analysis of the health effects of ETS was released by the Environmental Protection Agency (EPA) in January 1993.[7] In its report, EPA classified ETS as a Group A (known) human carcinogen under

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[4] National Research Council. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. National Academy Press, Washington, DC, 1986; U.S. Dept. of Health and Human Services. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General*. U.S. DHHS, Public Health Service, Office of the Assistant Secretary of Health, Washington, DC, 1986. DHHS Pub. No. (PHS) 87-8398.

[5] International Agency for Research on Cancer. *IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 38: Tobacco Smoke*. 1986. World Health Organization, Lyon, France. The IARC report found the available epidemiological evidence to be equivocal, but stated that "knowledge of the nature of mainstream and sidestream smoke, or the materials absorbed during passive smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens ... leads to the conclusion that passive smoking gives rise to some risk of lung cancer."

[6] National Institute for Occupational Safety and Health. *Environmental Tobacco Smoke in the Workplace: Lung Cancer and Other Health Effects*. Current Intelligence Bulletin 54. U.S. Dept. of Health and Human Services, NIOSH, 1991.

[7] National Institutes of Health, *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders; THe Report of the Environmental Protection Agency*, Monograph 4, NIH Publication No. 93-3605, August 1993, Washington, DC. (Here after referred to as the EPA Report.)

its carcinogen assessment guidelines and concluded that widespread exposure to environmental tobacco smoke presents a substantial public health risk. The EPA report's conclusions are summarized in the text box. EPA estimated that passive smoking is responsible for about 3000 lung cancer deaths per year in the adult, non-smoking (never smokers and long-ago former smokers) population, and poses a serious threat to the respiratory health of young children.

Environmental Protection Agency — 1993

Respiratory Health Effects of Passive Smoking

In adults:

- ETS exposure is responsible for approximately 3000 lung cancer deaths each year;
- ETS exposure has subtle, but significant respiratory health effects among nonsmokers, including chest discomfort and reduced lung function.

In children:

- ETS exposure results in 150,000 to 300,000 cases of bronchitis and pneumonia annually among young children up to 18 months of age;
- ETS exposure in children irritates the upper respiratory tract and reduces lung function;
- ETS exposure increases the prevalence of fluid in the middle ear and contributes to middle ear infection;
- ETS exposure increases the frequency of episodes and severity of symptoms in asthmatic children. Between 200,000 and 1,000,000 asthmatic children are affected by ETS.

The EPA report received widespread support from the public health community and from the larger scientific community. But it has been criticized by tobacco industry researchers and scientific consultants. A few independent statisticians and epidemiologists have also raised objections to EPA's statistical analysis of the ETS epidemiologic studies.[8] The Congressional Research Service

[8] The reader is referred to two congressional hearing at which researchers who support and criticize the EPA study testified: (i) U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health and the Environment, *Environmental Tobacco Smoke*, 103d Congress,

discussed some of these criticisms in an economic analysis of proposed increases in tobacco taxes.[9] In testimony before a Senate subcommittee, CRS concluded that "the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking."[10]

The controversy over the ETS studies stimulated subsequent requests of the Congressional Research Service to review the issue in more depth. This report is in response to those requests.

The report concentrates on the possible relationship between ETS and lung cancer in non-smokers. The study was carried out by a review and analysis of the major published literature, the preponderance of which is on ETS and lung cancer risk. The analysis was supplemented with a one-day meeting held in June 1995 of independent experts and representatives of the different agency and institutional views on possible health effects of ETS. One finding of the meeting was that detailed analysis of other potential health effects — heart disease and childhood respiratory illness — would require substantial additional efforts by CRS. Such efforts are beyond the resources of CRS. As a result, this report only briefly reviews current knowledge about those other topics.

This report is divided into four chapters. The first chapter summarizes the physical and chemical composition of ETS, and the evidence for ETS exposure and uptake among non-smokers. The second chapter examines the results of the various epidemiologic studies, with some emphasis on the implications of the

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1st Session, July 21, 1993; (ii) U.S. Congress, House Committee on Agriculture, Subcommittee on Specialty Crops and Natural Resources, *Review of the U.S. Environmental Protection Agency's Tobacco and Smoke Study*, 103d Congress, 1st Session, July 21, 1993. Three recent reviews in support of EPA's analysis are (i) Trichopoulos, D., *Principles and Practice of Oncology: PPO Updates Volume 8*, August 1994, pp. 1-8; (ii) *Consumer Reports*, January 1995; and (iii) Jinot, J. and S. Bayard, *Risk Analysis*, Vol. 15, No. 1, 1995, pp. 91-96. For a summary of the tobacco industry's criticism of the EPA report, see The Tobacco Institute, *EPA Report Scientifically Deficient*. Additional articles critical of EPA's analysis include: (i) The Alexis de Tocqueville Institution, *Science, Economics, and Environmental Policy: A Critical Examination*, August 1994, pp. 1-13; and (ii) Smith, C.J. et al., *Toxicologic Pathology*, Vol. 20, No. 2, pp. 289-303. For a critical review of the ETS-lung cancer risk that is written for the layman, see Huber, G.L. et al., *Consumers' Research*, July 1991, pp. 10-15, 33-34. Finally, see *Choices in Risk Assessment: The Role of Science Policy in the Environmental Risk Management Process*, Chapter 10, Workplace Indoor Air Quality, Regulatory Impact Analysis Project Inc., Washington, D.C. 1994, for a criticism of OSHA's proposed indoor air quality regulation.

[9] In their report, *Cigarette Taxes to Fund Health Care Reform: An Economic Analysis* (CRS Report 94-214 E, March 8, 1994), J.G. Gravelle and D. Zimmerman reviewed estimates of the economic costs that smokers impose on nonsmokers. The report reviewed the evidence of a passive smoking health risk because this is a potential component of the cost calculation. It concluded that (i) the evidence that passive smoking causes disease is far less certain than for active smoking, and (ii) the health costs of these potential passive smoking effects, if any, are likely to be quite small.

[10] Testimony of Drs. J.G. Gravelle and D. Zimmerman on May 11, 1994, before the Senate Committee on Environment and Public Works, Subcommittee on Clean Air and Nuclear Regulation.

dose-response trends for estimating the lung cancer risk among non-smokers. A discussion of confounding, smoker misclassification, and recall bias — the principal sources of uncertainty in the epi studies — is presented, including implications for the dose-response observations.

The third chapter discusses the potential lung cancer death risk of ETS including the consequences of an upward dose-response trend. This chapter also puts the potential risk of ETS in the context of other risks faced by the general population. The fourth chapter reviews the Occupational Safety and Health Administration's (OSHA) assessment of occupational ETS lung cancer risk, part of its proposed indoor air quality rule.[11]

The report also includes two appendices. Appendix A presents a brief overview of the evidence linking passive smoking with heart disease and childhood respiratory illnesses. Appendix B lists the principal ETS studies reviewed for this report.

[11] U.S. Dept. of Labor, Occupational Safety and Health Administration. Indoor Air Quality. Notice of proposed rulemaking; notice of informal public hearing. Federal Register, v. 59, no. 65, April 5, 1994. p. 15968.

ENVIRONMENTAL TOBACCO SMOKE

This section of the report briefly describes the chemical and physical characteristics of mainstream and sidestream smoke (the two major components of ETS) and discusses studies which have measured indoor ETS levels, and estimated ETS exposure and uptake among nonsmokers. Researchers have concluded that ETS contains most, if not all, of the carcinogenic and toxic compounds that are present in mainstream smoke. The studies also indicate that there is widespread exposure to ETS, and some measurable uptake of ETS by nonsmokers.

MAINSTREAM AND SIDESTREAM SMOKE[12]

Environmental tobacco smoke is a combination of mainstream smoke (MS) exhaled by smokers and sidestream smoke (SS) released directly from the burning tip of cigarettes. It is typically highly diluted. Mainstream smoke is comprised of small particles averaging 0.35-0.4 μm in diameter[13] (particle phase) and a mixture of gases (vapor phase). The particle phase includes several metals (e.g., cadmium and zinc) and a variety of non-volatile organic compounds of high molecular weight. The vapor phase includes numerous highly volatile compounds such as carbon monoxide and hydrogen cyanide.

Nicotine and many other semi-volatile constituents of tobacco smoke occur both in the particle phase and the vapor phase depending on their volatility and the prevailing conditions. These compounds tend to be present in the particle phase of highly concentrated inhaled MS, but evaporate into the vapor phase as exhaled MS rapidly dilutes during the formation of ETS.

Sidestream smoke is the primary contributor to ETS, providing most of the vapor phase and over half of the particles. It is produced by the same fundamental processes as MS and consists of the same chemical compounds including many known or suspected human carcinogens. However, SS is generated at lower temperatures and at a higher pH than MS, and as a result it has a different relative chemical composition.

Table 1 lists the concentrations of various compounds in both phases of MS delivered by unfiltered cigarettes, as measured by a standard smoking machine. The table also compares the amount of each compound delivered in MS and in SS by computing a SS/MS ratio.[14] These ratios indicate that, with the

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[12] For a more comprehensive discussion of the physical and chemical characteristics of mainstream and sidestream smoke, see M.R. Guerin et al. *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement*, 1992, Lewis Publishers, Inc., Chelsea, Michigan.

[13] One micron (m) = 1/1000 millimeter (mm).

[14] There is no standard method for collecting and analyzing SS, unlike MS. Researchers have used a variety of small chambers in which to confine the burning cigarette and collect the SS. These devices produce a somewhat artificial smoking environment compared to that associated with human smoking, and, of course, do not take into account the dilution that occurs during the

exception of hydrogen cyanide and organic acids, the majority of compounds are

TABLE 1. Comparison of Mainstream and Sidestream Smoke Deliveries for Selected Compounds

Constituent	Mainstream per Cigarette[a]	SS/MS Ratio
Mainstream vapor phase		
Carbon monoxide	10-23 mg	2.5-4.7
Carbon dioxide	20-40 mg	8-11
Benzene[b]	12-48 g	5-10
Acetone	100-250 g	2-5
Hydrogen cyanide	400-500 g	0.1-0.25
Ammonia	50-130 g	40-170
Pyridine	16-40 g	6.5-20
Nitrogen oxides	100-600 g	4-10
N-Nitrosodimethylamine[c]	10-40 ng	20-100
Mainstream particle phase		
Nicotine	1-2.5 mg	2.6-3.3
Phenol	60-140 g	1.6-3.0
2-Naphthylamine[b]	1.7 ng	30
4-Aminobiphenyl[b]	4.6 ng	31
Cadmium[c]	100 ng	7.2
Nickel[b]	20-80 ng	13-30
Lactic acid	63-174 g	0.5-0.7
Succinic acid	110-140 g	0.43-0.62

[a] The units are in milligrams (1 mg = 1/1000 g), micrograms (1 g = 1/1000 mg), and nanograms (1 ng = 1/1000 g).
[b] Known human carcinogen, according to EPA or IARC.
[c] Probable human carcinogen, according to EPA or IARC.
Source: National Research Council, 1986. Table 2-2.

released in greater quantities in SS than in MS. In its analysis of MS and SS emissions data, EPA found that all of the five known human carcinogens, nine probable human carcinogens, and three animal carcinogens are emitted at higher levels in SS than in MS, often by a factor of ten or more.

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formation of ETS.

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ETS COMPOSITION AND MEASUREMENT[15]

There is limited information on the chemical composition of ETS. Exhaled MS, which can contribute between 15 percent and 43 percent of the particulate matter in ETS, has yet to be characterized. There is also little data on the impact of dilution on SS emissions. During ETS formation, both SS and exhaled MS are diluted by many orders of magnitude and subsequently undergo physical transformation and alterations in chemical composition.

Numerous studies of the impact of smoking occupancy on indoor air quality have measured several ETS-related compounds of human health concern, including known and suspected carcinogens, in a variety of settings (e.g., residential, office, transportation, etc.). Researchers have concluded (1) that many of the potentially harmful compounds in SS are also present in ETS, and (2) that these ETS contaminants are found above background levels in a wide range of indoor environments in which smoking occurs. These studies indicate that the composition of ETS can be highly variable depending on the smoking rates, the amount and type of ventilation, contact with indoor surfaces, and a host of other environmental conditions.

Given that ETS is a complex mixture of thousands of compounds, many of which change chemically and physically over time, it is necessary to identify a chemical marker to represent the frequency, duration, and magnitude of ETS exposure. An ideal marker would be a compound that is specific to tobacco smoke, easy to measure, and that behaves similarly to ETS as a whole. Several markers have been identified, though none meets all these criteria. However, vapor phase nicotine and respirable suspended particles (RSP)[16] are both suitable indicators of exposure to ETS.

A variety of methods have been used to measure indoor nicotine and RSP levels in order to assess ETS exposure. Air sampling devices may be placed a specific indoor locations for varying periods of time (stationary sampling) or worn by individuals (personal monitoring). Researchers have also measured chemicals (biomarkers) in the blood and urine of ETS-exposed nonsmokers.

Tobacco combustion produces significant emissions of respirable suspended particles (RSP). There are a number of accepted methods that permit accurate measurement of RSP concentrations in indoor environments for sampling times ranging from seconds to several days. Studies have shown that RSP levels in smoking environments are usually higher than in non-smoking environments. Leaderer and Hammond conducted a large chamber study using smokers and

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[15] For more information on the chemistry of ETS and on chemical markers for ETS, see EPA Report, chapter 3; and Guerin et al., 1992.

[16] Respirable suspended particles (RSP) refers to particles that are small enough to reach the deepest recesses of the lungs during inhalation. There is some disagreement among researchers as to the upper size limit for RSP. Some investigators use a conservative value of 3 m, others use values of 10 or 15 m. However, if one is using RSP as a marker for ETS, choosing among these values is largely irrelevant, because most ETS particles are less than 1 m.

reported an average RSP emission rate per cigarette of 17.1 mg.[17] RSP emission rates among different brands of cigarettes were similar.

Respirable suspended particles are also generated by other types of combustion. At low smoking and high ventilation rates, it might be difficult to distinguish ETS-associated RSP from a background of RSP from other indoor sources (e.g., kerosene heaters) or even outdoor sources. However, studies by Repace indicate that the fraction of indoor RSP attributable to smoking is typically 80 to 90 percent of the total RSP.[18]

Vapor phase nicotine is the most common ETS marker. Nicotine is unique to tobacco and can be reliably measured using a variety of methods. Average indoor air concentrations typically range from 1 to 10 micrograms per cubic meter ($\mu g/m^3$). Several studies have shown that weekly nicotine concentrations are highly correlated with the number of cigarettes smoked. One of these studies also reported a strong correlation between weekly nicotine concentrations and RSP levels in smoking households.[19] The RSP-to-nicotine ratio in this study was approximately 10:1, which is similar to the ratio seen in chamber studies and other field studies, including a recent California State report.[20]

Nicotine is not an ideal ETS marker because it is readily adsorbed onto surfaces, thus reducing its concentration relative to other ETS components as ETS ages. Some studies have demonstrated that vapor phase nicotine is depleted from a smoking environment more rapidly than the particulate portion of ETS. This could lead to an underestimation of ETS exposures. Nicotine also evaporates from surfaces onto which it has been adsorbed, which results in measurable concentrations even in the absence of active smoking. The affinity of nicotine for surfaces may limit its use as an ETS marker in environments where ETS concentrations are very low. However, under normally encountered smoking rates, the uncertainties associated with nicotine's high adsorption rate are likely to be small.

ETS INDOOR AIR CONCENTRATIONS AND EXPOSURE

Numerous studies have measured concentrations of nicotine and RSP in a variety of indoor environments. These studies employed a range of sampling devices, sampled over varying timeframes (from minutes to days), and included highly variable information on various factors affecting the measured

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[17] Leaderer, B.P. and S.K. Hammond. *Environ. Sci. Technol.*, Vol. 25, 1991, p. 770-777.

[18] See, for example: Repace, J.L. Tobacco Smoke Pollution. In *Nicotine Addiction, Principles and Management.* Orleans, T. and A.H. Lowrey, eds. Oxford University Press, New York, 1993.

[19] Leaderer, B.P. and S.K. Hammond, 1991.

[20] The California Air Resources Board report, *Toxic Volatile Organic Compounds in ETS: Emissions Factors for Modeling Exposures of Californain Populations*, was prepared by the Lawrence Berkeley Laboratory and concluded that nicotine and ETS-RSP behave similarly.

concentrations, such as number of cigaretts smoked and ventilation rates. EPA summarized much of this information in its report, to which the reader is referred for more detailed information.[21]

Stationary Air Samplers

Most of the studies used stationary air samplers. Although the results were highly variable, nicotine and RSP concentrations in smoking environments were consistently higher than in non-smoking environments. Table 2 shows the range of average values obtained in these studies. The minimum and maximum values are also presented in parentheses. Only studies reporting sampling times over four hours were included in the data on residential and office settings so as to more closely approximate occupancy time. Since occupancy time in restaurants is likely to be shorter than four hours, data from studies using shorter sampling times were included in the table.

TABLE 2. Indoor Nicotine and RSP Concentrations with Smoking Occupancy: Range of Average Values Reported (Min - Max Values)

Location	Nicotine (g/m^3)	RSP (g/m^3)[a]
Residential	2-11 (<1-14)	18-95 (5-560)
Office	1-13 (<1-35)	<5-62 (<5-90)
Restaurant	6-18 (<1-70)	35-986 (10-1370)

[a] RSP levels associated with smoking occupany were calculated by subtracting background RSP levels associated with non-smoking occupancy.
Source: Figures 3-7 and 3-8, EPA, 1992.

The summary nicotine data in the table indicate that average concentrations in residences with smoking occupancy range from 2 $\mu g/m^3$ to 11 $\mu g/m^3$, with high values up to 14 $\mu g/m^3$ and low values down below 1 $\mu g/m^3$. Offices with smoking occupancy have average nicotine concentrations that are similar to those in residences, but with significantly higher maximum values. The data from restaurants show even higher maximum values. With regard to RSP concentrations, there is also broad overlap in the average values obtained from residential and office environments. However, the data from restaurants show a much wider range of values.

In a recently published study, Hammond and coworkers measured average weekly nicotine concentrations at 25 diverse worksites including fire stations, newspaper publishers, textile dyeing plants, and a variety of manufacturing

[21] EPA Report, chapter 3.

companies.[22] Between 15 and 25 samplers were placed in each worksite. Worksite smoking policy had a significant effect on the nicotine concentration. The median[23] nicotine level in open-plan offices that allowed smoking was 8.6 $\mu g/m^3$, but only 1.3 $\mu g/m^3$ in worksites that restricted smoking to designated areas. In worksites that banned smoking, the median nicotine level was 0.3 $\mu g/m^3$.

Guerin and Jenkins measured the concentrations of ETS constituents, including nicotine and RSP, in "typically encountered" residential and occupational indoor settings and found that low-level concentrations were much more common than higher-level concentrations.[24] These results reflect the fact that the researchers included a significant number of non-smoking and smoking-restricted sites. Very high concentrations were generally found in enclosed areas designated for smoking, and in poorly ventilated areas where smoking intensity was high.

Personal Monitors

Measurement of indoor air concentrations of ETS components indicates the potential for exposure, but actual exposure also depends on the amount of time spent in a particular environment. The amount of exposure will depend on the individual's circumstances. A woman who lives with a nonsmoker but works in an office with smokers will receive most of her ETS exposure at work, whereas someone who lives and works with smokers may receive the majority of her exposure in the home where more time is spent.

Personal monitoring allows researchers to estimate individual exposure. Study participants wear a monitor that continuously samples and records the concentration of air contaminants to which individuals are exposed in the course of their daily activities. If subjects use different monitors in different indoor environments (e.g. home vs. workplace) and record the amount of time spent in each setting, then researchers can calculate the contribution of each environment to total exposure.

To date, few studies have measured ETS exposure to nicotine and RSP using personal monitors. Limited published data on nicotine show a wide range of ETS exposures in indoor environments with smoking occupancy, with average concentrations ranging from less than 5 $\mu g/m^3$ up to 40 $\mu g/m^3$. Other personal

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[22] Hammond, S.K. et al. *J. American Medical Association*, v. 274, no. 12, 1995. p. 956-960.

[23] The median value is the mid-point of a range of measurements. Half of the values are less than the median, half are greater than the median.

[24] For more information, see Guerin et al., 1992; Guerin, M.R. and R.A. Jenkins. *Recent Advances in Tobacco Science*, Vol. 18, 1992, p.95-114; and Guerin, M.R. Environmental Tobacco Smoke Exposure Assessment. Paper presented at Japan Indoor Air Research Society, April 1993. Sponsored by U.S. Dept. of Energy. NTIS/DE93015521.

monitor studies found that ETS exposure increased RSP levels between 18 $\mu g/m^3$ and 64 $\mu g/m^3$.[26]

It is difficult to assess the ETS contribution to nicotine and RSP levels for each indoor environment using these data. In many cases, study participants wore the same monitor for 24 hours, and the reported nicotine and RSP levels represent 24-hour average values. These values may underestimate the contribution of some non-residential indoor environments as they include home sleeping hours when presumably there was little if any ETS exposure.

Unpublished data from a recent multi-city study using personal monitors suggest that typical exposures are low relative to estimates obtained using stationary air samplers. This large study, conducted jointly by Oak Ridge National Laboratory and R.J. Reynolds Tobacco Company, recruited approximately 100 nonsmokers in each of 16 cities nationwide. Study participants were provided with two monitors — one to wear at work and the other for the remainder of the 24-hour period — and required to keep a detailed written record of their activities. In addition to nicotine and RSP, the monitors measured five other ETS constituents.

The average nicotine concentration in 415 smoker-occupied homes was 2.16 $\mu g/m^3$, with a median level of 0.68 $\mu g/m^3$, indicating that most participants received relatively little ETS exposure. The average and median nicotine levels in workplaces without smoking restrictions were 2.77 $\mu g/m^3$ and 0.58 $\mu g/m^3$, respectively. Researchers calculated total daily exposure to nicotine in each indoor environment by multiplying the average nicotine concentration by duration of exposure and breathing rate. Total daily nicotine exposure in smoker-occupied homes was 6.8 μg per day (μg/day), compared to a value of 5.8 μg/day for workplaces without smoking restrictions.

The study's authors suggested two explanations for the fact that average nicotine concentrations recorded in this study lie at the bottom end of the ranges reported in earlier studies. First, fewer smokers are lighting up in the presence of nonsmokers, a response to changing societal attitudes toward smoking. Second, nonsmokers are spending less time in obviously smoky environments. Nonsmokers who come in contact with smokers may receive relatively little exposure depending on their proximity to the smoker and the length of time spent in that indoor environment.

Noting the tobacco industry's involvement in the study, critics claim that it underrepresented the amount of ETS exposure among nonsmokers. The study sampled a disproportionately low number of smoker-occupied workplaces. Out of 1,356 workplaces sampled, only 168 (12.4 percent) allowed smoking without restriction. National estimates of workplace smoking prevalence suggest that a significantly higher percentage of workplaces allow smoking (see later section on occupational ETS exposure). However, it is not possible to determine whether the recruitment procedures used in the study led to the

[26] EPA Report, tables 3-5 and 3-6.

selection of participants whose ETS exposure in smoker-occupied indoor environments was significantly below average exposure levels for nonsmokers nationwide.

Biomarkers

The presence of a biomarker in the blood or urine provides direct evidence of ETS exposure and uptake. The relationship between the biomarker and exposure is complex due to many environmental and physiological factors. The most commonly used and widely accepted ETS biomarker is cotinine, the major metabolite of nicotine inside the body. Nicotine has a half-life of about 2 hours in the blood and is metabolized to cotinine and excreted in the urine. Cotinine has a half-life of approximately 20 hours in smokers, somewhat longer in ETS-exposed nonsmokers, which makes it a good indicator of ETS exposure and uptake over the previous two days.

Studies show that blood and urine cotinine levels in ETS-exposed nonsmokers are generally higher that those in nonsmokers reporting no ETS exposure, but far lower than the levels of cotinine in smokers. Comparisons of cotinine levels in smokers and nonsmokers indicate that ETS-exposed nonsmokers receive approximately 0.7 percent of the nicotine dose of an average smoker.[26] Cotinine levels in nonsmokers have also been found to increase with self-reported ETS exposure. There is considerable variation in cotinine levels among smokers and ETS-exposed nonsmokers because of individual differences in the uptake, metabolism, and elimination of nicotine.

ETS CANCER RISK

The EPA classified ETS as a carcinogen based on the chemical similarities between inhaled MS and ETS, and evidence of ETS exposure and uptake by nonsmokers. Studies indicate that tobacco smoke is a lung carcinogen even at the smallest exposures to active smoking, and the risk increases with exposure, as measured either by number of cigarettes smoked per day, or years of cigarette smoking. According to the EPA, exposure to ETS, which is qualitatively similar to MS, therefore, should also increase the risk of lung cancer, and the evidence of widespread exposure to, and uptake of, ETS components in the general population is sufficient to conclude that ETS is a lung-cancer hazard.[27]

A few researchers have challenged the classification of ETS as a known human carcinogen based on its relationship to MS. They point to the fact that MS contains chemicals at concentrations of up to one million times those found in ETS, and that more of the chemicals are in the particle (tar) phase of MS. Differences between passive smoking (normal inhalation) and active smoking

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[26] Jarvis, M.J. *Mutation Research*, Vol. 222, 1989. p. 101-110.

[27] See, for example, testimony presented by Dr. Douglas Dockery, Harvard School of Public Health, on July 21, 1993, before the House Committee on Agriculture, Subcommittee on Specialty Crops and Natural Resources.

(deep inhalation) also affect the degree of exposure to vapor phase constituents and the deposition of particles inside respiratory passageways. Based on these considerations, an ETS chemist concluded that the evidence for ETS carcinogenicity remains questionable.[28]

Asserting that ETS is a lung carcinogen leaves unanswered the question: How great a cancer risk does passive smoking pose? Researchers have used nicotine measurements to calculate ETS exposure in terms of cigarette equivalents, by estimating the number of cigarettes one would have to smoke to receive the same amount of nicotine as breathing ETS in a particular environment for a given period of time.[29] For example, the amount of nicotine inhaled by a nonsmoker working in a relatively smoky restaurant for eight hours is equivalent to smoking one-eighth of a cigarette.[30]

Cigarette equivalents calculated for some of the known carcinogens in ETS yield much higher values because these compounds are emitted at higher levels in SS than in MS (see Table 1). About three times as much nicotine is emitted in SS as in MS, whereas approximately 30 times as much 4-aminobiphenyl (4-ABP). Thus, a description of exposure in nicotine cigarette equivalents underestimates exposure to a known carcinogens in tobacco smoke by a considerable margin.[31]

The cigarette equivalent approach can also be applied to cotinine data. If, as stated above, cotinine levels in ETS-exposed nonsmokers average 0.7 percent of the levels found in smokers, and if one assumes that the average smoker smokes 19 cigarettes a day,[32] then the amount of nicotine to which the average ETS-exposed nonsmoker is exposed is roughly equivalent to smoking one-eighth of a cigarette a day.

There are significant uncertainties in using cigarette equivalents to try to quantify ETS cancer risk. Estimates of ETS exposure using cigarette equivalents vary enormously depending on the compound chosen. Researchers

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[28] Testimony presented by Dr. Michael Guerin, Oak Ridge National Laboratory, at the July 21 ETS hearing.

[29] The formula for cigarette equivalents = amount from ETS exposure/amount from smoking one cigarette.

[30] Assumes an average nicotine concentration of 18 g/m^3. Exposures longer than 8 hours would lead to proportionately higher cigarette equivalents, as would higher breathing rates resulting from physical exertion at work. Based on calculations presented in Hammond et al., 1995.

[31] Recent newspaper advertisements by R.J. Reynolds Tobacco Company stated that nonsmokers are exposed to only slightly more than one "cigarette equivalent" a month in the workplace. However, this statement is misleading as it refers to nicotine cigarette equivalents and therefore underestimates exposure to many other toxic and carcinogenic compounds in ETS.

[32] U.S. Centers for Disease Control. *Morbidity and Mortality Weekly Report*, Vol. 41, 1992. p. 354.

do not know how the levels of these individual compounds relate to overall ETS exposure, or exposure to those ETS constituents that may be linked to lung cancer. Indeed, they do not know which ETS constituents are responsible for lung cancer and other health effects attributed to ETS exposure. Although 4-ABP is a bladder carcinogen, it does not appear to be associated with lung cancer. Finally, the contrasting breathing patterns of active and passive smokers may strongly influence the degree of exposure and uptake of various tobacco smoke constituents in the lungs of smokers and nonsmokers.

In order to estimate ETS lung cancer risk using cigarette equivalents researchers assume that there is a linear relationship between exposure (number of cigarettes smoked a day) and cancer risk that extends from the relatively intense exposures typical of active smoking down to the much lower exposures associated with passive smoking. EPA uses this type of straight-line extrapolation from high exposures down to zero exposure in all its cancer-risk assessments but researchers do not know the actual shape of the exposure-risk relationship for passive smoking and lung cancer.

ETS AND LUNG CANCER - EPIDEMIOLOGY

INTRODUCTION

This chapter presents a review of the epidemiology evidence for the possible relationship between ETS and lung cancer, based on results for spousal exposure. The review will particularly address the dose-response relationship between ETS exposure and lung cancer risk reported in many of these studies. Results of these studies will be presented first, followed by a discussion of the uncertainties associated with the analyses. The section will conclude with a discussion of the principal sources of possible alternative explanations of the results given in the studies. Attention is given to confounders and misclassifications errors.

BACKGROUND

The chemical similarities between mainstream and sidestream smoke and the association of active smoking with lung cancer are reasons for a possible relationship between ETS and lung cancer. But, they do not prove the relationship, since ETS is substantially diluted and aged compared to even low levels of active smoking. It is possible that ETS exposures are too small to be the cause of lung cancer in any meaningful sense; it is possible that some exposures are large enough to have an effect and others are not; and, it is possible that even a very limited exposure could cause some disease.

Epidemiologic studies are statistical studies of actual populations that are aimed at testing those hypotheses. By and large, these studies use as a measure of exposure to ETS, marriage to a smoker.

With only a few exceptions, these studies are of the "case-control" type. A group of non-smoking women ill with lung cancer (cases) are questioned as to the smoking status of their husbands and a comparable group from the population at large (controls) are also questioned. If a larger fraction of the cases have been exposed than of the controls, the risk of ETS is positive. The risk is usually expressed as a relative risk ratio (or odds ratio), which is the ratio of exposed to unexposed among the cases, divided by the ratio of exposed to unexposed among the controls. If the risk ratio is, for example, 1.2, that means that exposure to ETS increases the risk of lung cancer by twenty percent. (Such a risk would be quite small in absolute terms, however, because lung cancer among nonsmokers is quite rare).

An alternative but rarely used approach is a cohort study, where a large group in the population is followed and the exposure levels of those who develop the disease and those who don't are compared. Cohort studies are superior in theory to case control studies, but because lung cancer is extremely rare among nonsmokers thus requiring a large group, and because of the lengthy period of time required, these studies tend to be rare.

Some studies have also asked questions regarding the degree of exposure, by asking subjects how long and/or how much their husbands smoked. If there is an effect of ETS on lung cancer, it should be greater with greater exposure measured by either intensity or duration. As statistical studies, the interpretation of the findings in these studies are subject to many limitations of statistical inference, and these limitations have been the subject of considerable controversy in the debate on ETS and lung cancer.

First, only a sample of the population is studied, and it is possible that any relationships observed are due to chance. Statistical results are always qualified by their degree of statistical significance, which is merely another way of measuring the probability that the results hold for the entire population and not just the particular sample under study. This measure is often expressed as a confidence interval (CI), which is centered on the actual measure of risk. For example if a 95 percent confidence interval is given, it means that there is a 95 percent chance that the truth lies between the two limits. There is a 5 percent chance that the answer falls outside the interval: 2 and 1/2 percent that it is larger and 2 and 1/2 percent that it is smaller. If the entire confidence interval falls in the positive risk range (the lower limit is at or above one), then the study would be interpreted as showing a positive risk at the 95 percent level, and we would normally accept the hypothesis (were there no other problems) that ETS poses a risk.

For large samples, the confidence interval will be narrow; for small samples it will be wide. Thus, in a small sample, the measured risk would have to be very high to achieve statistical significance. Indeed, researchers also sometimes refer to the power of a study to detect a small risk -- small studies have less power than large ones. The limited ability of small studies to accurately inform us of the true risk is important to keep in mind in evaluating the results. For example, seven of the eleven U.S. studies reviewed by EPA had only about a 20 percent chance of detecting a statistically significant risk of 50 percent (i.e., risk ratio = 1.5) using a 95 percent confidence interval.

Over time, certain conventions for the level of statistical significance have developed; 95 percent is common. Statisticians are faced with two types of potential error: type I, accepting the hypothesis when it is not true, and type II, failing to accept the hypothesis when it is true. Any convention that is adopted balances between these errors -- the more you minimize one error, the greater the likelihood of the other error. If a standard convention for statistical significance is chosen, then small studies are more likely to be subject to type II error. However, there is no objective standard for determining what level of significance is necessary to accept a hypothesis; one is always dealing with some degree of probability.[33]

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[33] There has been some criticism about the standard used by the EPA, which was a 90 percent confidence interval rather than a 95 percent interval. Critics have complained that standard was atypically chosen to ensure statistical significance in the over all weighted average of the EPA's combined studies. The EPA has responded with a justification for their choice. This issue is a procedural matter, and not one that relates directly to the evidence.

In addition to considering sampling error in determining whether the results of a study are valid, there are other potential problems. Questions of statistical significance and statistical power relate only to the issue of sampling from a population. There are other potential problems with interpreting the results of studies, which primarily have to do with two issues: (1) are there other factors independently associated with both the development of lung cancer and exposure to ETS that could account for the relationship? and (2) are subjects properly identified into the correct groups -- for example, are all exposed cases truly ill with primary lung cancer, truly nonsmokers, are they all truly exposed to ETS, or have they correctly reported their exposure level? Some studies make considerable efforts to control for other factors and to verify the classification of subjects into the proper categories; others do little in that regard. Even the best of studies, however, face practical limitations on their abilities to verify and control.

Some critics have also suggested that there is a publication bias -- a tendency for studies that yield positive results -- those which support the hypothesis -- to be published.[34] This behavior does not necessarily mean a deliberate bias on the part of editors and researchers. For example, in some cases a researcher might study many potential cancer-causing factors and simply not mention those that do not support the hypothesis being tested. If this tendency occurs, then published studies will be biased in favor of positive results. For that reason, large studies that are aimed at the beginning towards studying ETS may be more reliable.

Given the limitations of statistical analysis, what standards are used to evaluate the results, even when results are statistically significant? In 1964, a group of experts was brought together by the Surgeon General to define a set of criteria for causal inference. These criteria, which are often referred to as the Bradford Hill criteria, are widely used by epidemiologists today and are summarized in the box below.[35]

Epidemiologists typically await the results of several studies before weighing all the available evidence for a causal relationship. The first criterion is the strength of the association. How large is the relative risk? Hill argued that a strong association — usually taken to mean a risk ratio of at least three — is more likely to be causal than a weaker association because if it was due to confounding or some other bias, this effect would have to be large enough that it would presumably be evident. On the other hand, weak associations are more likely to be explained by undetected biases. The fact that an association is weak, however, does not rule out a cause-effect relationship. The strength of an association is not a biologically consistent feature but rather a characteristic that depends on the relative prevalence of other causes.

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[34] LeVois, M.E. and Layard, M., *Regulatory Toxicology and Pharmacology*, Vol.21, 1995, p.184-191.

[35] For a more detailed discussion of the Hill criteria, see Rothman, K.J., *Modern Epidemiology*. Little, Brown and Co., Boston, Massachusetts, 1986.

Criteria for Causal Inference

Strength of association: How big is the relative risk?

Consistency of association: Do similar studies by other researchers yield similar results?

Dose-response relationship: Does the risk increase with increasing exposure?

Temporal relationship: Does exposure precede the onset of illness?

Biological plausibility: Does the association make sense in light of biological knowledge?

Coherence: Is the association consistent with existing knowledge about the natural history of the disease?

Specificity of association: Is exposure linked to a single disease?

The second criterion is consistency of association; whether similar studies by other researchers yield similar results. If the relative risk is small, then the evidence of a dose-response relationship — the third criterion — becomes very important in attempting to determine causation. Does the risk increase with increasing ETS exposure?

The remaining criteria have more to do with the underpinnings of the basic theory rather than statistical matters, and are addressed elsewhere in the paper.

OVERALL EFFECTS AND PREVIOUS STUDIES

In performing its assessment of the possible contribution of ETS exposure to lung cancer in non-smokers, EPA relied on 31 epidemiology studies published over the period 1981-1992.[36] These studies, which were carried out in several countries in addition to the United States, examined the possible lung cancer-ETS linkage using predominantly case-control methods to measure the relative risk of developing lung cancer due to exposure to ETS. In all cases, the primary objects of the study were non-smoking women subjected to ETS from a smoking spouse. The studies relied primarily on questionnaires to the case and control group members, or their surrogates, to determine ETS exposure and other information pertinent to the studies. All of the studies reported an average relative risk for the entire case group and several reported relative risk as a function of the dose of ETS reported to have been received by the case group members. In addition, 95 percent confidence intervals for the relative risk values were generally provided.

[36] EPA Report, p.114.

Nearly all of the debate about the possible health effects of ETS, to date, has focused on overall relative risk. The EPA considered 31 studies -- including 11 from the U.S. -- in its analysis of ETS and lung cancer risk. Using a method of combining studies, called meta-analysis, it concluded that there is an overall relative risk of 1.19 for developing lung cancer for female non-smokers in the U.S. with a 90 percent confidence interval of (1.04, 1.35). In a 1986 report assessing the health effects of ETS, the National Research Council estimated a relative risk of 1.32 , with 95 percent confidence limits of (1.16,1.52), for female non-smokers in this country.[37] Both the NRC and the EPA concluded after further analyses of these results that a causal relationship existed between ETS and lung cancer in non-smokers. The earlier NRC study, however, had available a much smaller number of studies (9 overall and 3 from the United States).

The EPA report then used this result to calculate overall risk (annual deaths) due to exposure to ETS, assuming the risk was uniform among nonsmokers.

For a variety of reasons, EPA's conclusions have been controversial. While many in the scientific community have accepted the EPA conclusions, other have criticized them. First, the findings in the studies were mixed, and of the 30 studies examined by EPA (one Japanese study could not be used because of the presentation of data), 24 found an increased risk, though only five were statistically significant at the 95 percent level, and six actually found a negative risk (with one statistically significant). Of the eleven U.S. studies, eight found a positive risk and three found a negative risk, though none was statistically significant.

These studies originally considered by the EPA and their confidence intervals are shown in figure 1 (next page), ordered by increasing level of risk. Note that large studies have narrow confidence intervals and small studies have very wide ones. They incorporate a downward correction for a certain type of bias -- smoker misclassification -- that has been of some concern in evaluating the results of these studies. Note also that the EPA examined studies and ranked them in tiers with respect to their usefulness in four tiers; the fourth tier studies were deemed too poor to use in the analysis. (These studies are Lui, Wu-Williams, Geng, and Inoue; none was in the U.S.).

Figure 1 also includes four U.S. studies[38] that appeared after the EPA cutoff, one of them the final version of the Fontham, et.al., (hereafter Fontham) study, which is the expanded and refined version of the original Fontham study included in the EPA report. (Thus, the original Fontham study should be subsumed by the new one and the final study should not be viewed as wholly new evidence). The risk estimate in the final Fontham study is similar to the original one included in the EPA study, but attains statistical significance

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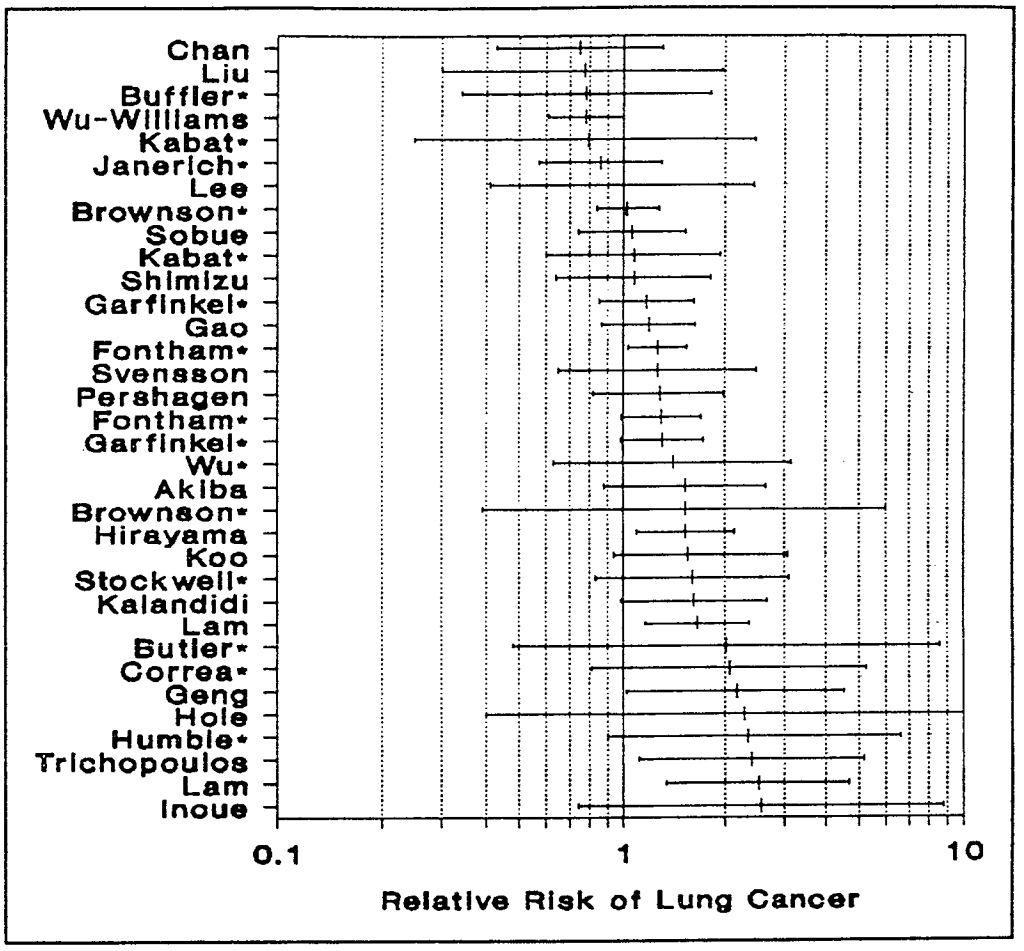
[37] NRC Study, p.231.

[38] Brownson, R.C., et.al.; Fontham, E.T.H., et.al.; Stockwell, H.G., et. al.,; and Kabat, G.C., et.al.

Figure 1: Residential Epidemiologic Studies of Passive Smoking and Lung Cancer



Means plus 95 percent confidence intervals. Data from Tables 5-2 and 5-5, U.S. EPA, 1992.
* U.S. studies.

because of its larger numbers of observations. The other three new studies show, in one case, no effect (the Brownson, et,al,. hereafter Brownson study) in the other cases a positive effect that is not statistically significant (Stockwell,et.al., hereafter Stockwell, Kabat, et.al., here after, Kabat), and in the case of the Kabat study, very small.

None of these new studies was adjusted for smoker misclassification and their risk ratios would presumably be smaller if the standard EPA adjustment were made. The Brownson results would probably show a negative risk overall, the Stockwell results a smaller positive risk, which would remain statistically insignificant, and the Kabat result might disappear or even be negative). The EPA did adjust the original Fontham study, but only by a small amount because of the care taken in testing for misclassification in that study. In the final

Fontham study, a small adjustment could render the overall Fontham results statistically insignificant at the 95 percent level.

Simply comparing results of different studies is of limited value, since, as noted above, small studies provide limited information because of sampling error. For that reason, the EPA combined the studies (through a meta-analysis) to yield the overall estimate of a risk of 1.19 percent. The rationale behind combining studies is simple: if there are a lot of small studies that each do not obtain statistical significance, but each have a positive effect, then if they could have been studied as one group of observations, the test would have been more powerful. Combining the studies takes into account the probabilities associated with the whole body of studies.

Although this approach is valid, and is superior to just counting up the studies, it still does not entirely clarify the risk. Even when overall risk is considered, it is a very small risk and is not statistically significant at a conventional 95 percent level. Moreover, problems of bias and confounding that are mentioned above (and will be discussed subsequently) still occur in most studies; they probably occur to some extent, but with different degrees of seriousness, in all of the studies. Some studies were much more careful in controlling for other factors that might influence the study's results.

The new studies, including the very large Brownson study, did not clarify the existence of a risk. Indeed, they complicated the interpretation of the evidence, since the two largest U.S. studies -- Fontham and Brownson - found in one case a positive risk that was barely statistically significant and the other no risk at all.

For these and other reasons, the conclusions in the EPA study have generated considerable controversy. While receiving support from a segment of the scientific community, others have registered criticism focusing on the uncertainty inherent in such low risk values and argued that there were potentially other explanations for these results if indeed they were not due to chance alone.[39]

Missing from most of these analyses was any emphasis on the dose-response relationships observed in many of the studies, traditionally an issue that is considered in establishing causality. In many studies, respondents were questioned as to the degree of exposure, either in number of cigarettes per day the husband smoked, number of years the husband smoked, or a multiple (pack years). If there is a risk from ETS, it would be expected to rise with exposure.

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[39] See for example *Review of the U.S. Environmental Protection Agency's Tobacco and Smoke Study*, hearing before the Subcommittee on Specialty Crops and Natural Resources, Committee on Agriculture, U.S. House of Representatives, July 21, 1993, Washington, DC; and Smith, Carr J., et.al.

Of the 31 studies reviewed by EPA, 17 presented data on the variation of relative risk as a function of ETS exposure levels.[40] EPA carried out an analysis of these studies including the calculation of pooled risk estimates, confidence intervals and trend tests.

EPA also looked at high exposure levels to see if there was a significant effect. EPA went on to say that "It appears that relatively high exposure levels are necessary to observe an effect in the United States, ..."in its assessment of dose response trends. As noted above, positive trends were viewed as evidence of an effect, but no further consideration of dose-response relationships was given in the EPA analysis.

In particular, EPA did not use dose-response relationships in its estimates of population risk. If risk does vary by exposure level, then this assumption may not give a true picture of the risk distribution of developing lung cancer from ETS.

Attention to the dose-response trends is particularly important because of the possibility that much of the risk may be concentrated at the largest, integrated, ETS exposure levels (daily ETS exposure times its duration). If so, such an observation could have substantial consequences for possible mitigation actions. In addition, dose-response analyses can be used as an additional test of the possible role of confounders and misclassification biases in explaining reported ETS health risk.

Also, most analyses of other potential environmental hazards consider the effect of dose levels when assessing the possibility of public health dangers and policy response. Regulations to protect the public from such hazards usually have exposure limitations rather than banning exposure altogether. Given the potential importance of dose-response relationships for ETS and the extensive comments that have already been made on the EPA analysis of the average relative risk, this analysis has chosen to concentrate on the dose-response issue.

Turning to more specific measures of exposure does, however, introduce a potential new form of bias -- recall bias. The more specific the question about exposure, the more precise the measure, but the less accurate the recall. That is, there is likely to be a very small error rate in reporting marriage to a smoker, but there could be a significant error in reporting actual amounts of exposure, such as numbers of cigarettes smoked by a spouse, particularly in the past.

In reviewing the dose-response analysis of ETS, the 17 studies listed in the EPA report which reported dose-response data along with three other studies, not considered by EPA, which also examined the dose-response relationship, were examined.[41] These three, Brownson, Stockwell, and Kabat, appeared after

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[40] EPA Report, p.144.

[41] See Appendix B for list of studies used in the table.

the EPA report was published. The Fontham study was only partially completed when included in the EPA analysis.

All but two of the studies used a case-control method. The others were cohort studies. Cases were selected from various sources of lung cancer patients or those who recently died of lung cancer, and the controls were chosen using various random selection techniques. Only individuals who stated that they had never smoked, or, in some cases, had quit several years prior to the study, were selected as participants in the case and control groups.

The participants were interviewed directly if possible -- a number of the cases in nearly all of the studies required surrogates -- to determine exposure to ETS and other information relevant to the studies. For example, data on age, educational level obtained, occupation, and other factors were obtained to permit matching of controls and cases and to eliminate as many factors as possible that may compromise the results. In addition, many of the studies attempted to obtain data on dietary habits to control for these potential confounders in calculating the relative risk values. More will be presented on this issue below.

Finally in all of these studies, the cases and controls who stated they had been exposed to ETS were asked for information about the extent of exposure. In most of the studies, this information was provided separately for number of cigarettes per day and for duration of exposure. In a few of the studies, an integrated exposure level, packs of cigarettes per day times years exposed at that daily level, was provided.

There are two final caveats to interpreting these data. First, unlike the overall results presented earlier, these measures have no downward correction for smoker misclassification. Second, by segmenting the observations in the study, the numbers become smaller and the tests less powerful (less able to detect a statistically significant risk).

RESULTS

The results are summarized in tables 3, 4 and 5 on the following two pages. Each study used standard statistical methods to carry out the analyses. Relative risk values (odds ratios) -- labeled RR in the tables -- and 95 percent confidence levels (in most studies) -- labeled CI in the tables -- were calculated using logistic regression techniques or related methods. Those confidence intervals marked with an * are at the 90 percent level. Average relative risk values and confidence intervals were measured along with those at various exposure levels. Only the latter are reported in the tables.

The tables are organized by exposure measures. Table 3 is cigarettes per day, table 4 is pack-years (packs per day times years at that level), and table 5 is smoker years. All but one of the studies in the last category also reported results in terms of one of the other two exposure measures. In the table, exposure levels were adjusted from the reported levels when possible to keep the

studies as comparable as possible. The key to the numbers in the column marked study is in Appendix B.

Table 3 -- ETS Dose-Response Observations -- (Cigarettes per Day)

Study	Exposure	RR	95% CI	Study	Exposure	RR	95% CI
1	1-20	1.93	(1,29,2.88)	2	1-20	1.95	(1.13,3.36)
	≥21	2.07	(1.07,4.01)		≥21	2.55	(1.31,4.93)
3	1-19	1.27	(0.85,1.89)	4	1-19	1.41	(1.03,1.94)
	≥20	1.10	(0.77,1.61)		≥20	1.93	(1.35,2.74)
5	1-10	0.82	(0.42,1.61)	6	1-19	1.3	(0.7,2.3)*
	≥11	1.06	(0.49,2.30)		≥20	1.7	(0.9,3.2)*
7	1-19	1.12	(0.7,1.8)	8	1-9	1.40	(1.1,1.8)
	≥20	2.11	(1.1,4.0)		10-19	1.97	(1.4,2.7)
					≥20	2.76	(1.9,4.1)
9	1-20	1.8	(0.6,5.6)*	10	1-20	1.54	(0.8,3.0)
	≥21	1.2	(0.3,5.2)*		≥21	1.71	(0.9,3.4)
11	1-20	1.76	(1.0,3.2)	12	1-15	1.02	(0.6,1.8)
	≥21	1.19	(0.5,3.0)		≥ 16		(1.0,9.5)
19	5-19	1.58	(0.4,5.7)*				
	≥20	3.09	(1.0,11.8)*				

Table 4 - ETS Dose-Response Observations -- (Pack-Years)

Study	Exposure	RR	95% CI	Study	Exposure	RR	95% CI
14	1-40	1.18	(0.44,3.20)	15	1-39.9	1.02	(0.82,1.26)
	≥41	3.52	(1.45,8.59)		≥40	1.43	(1.07,1.91)
16	1-40	0.70	(0.52,1.18)	17	1-24	0.71	(0.37,1.35)
	≥41	1.30	(1.0,1.7)		25-49	0.98	(0.47,2.05)
					≥50	1.10	(0.47,2.56)

Most of the studies report a small but positive effect which increases as exposure level increases. Three of the studies show effects of less than 10 percent excess risk at the highest exposure levels, and four of the studies show no indication of a trend of increasing risk with increasing exposure. In addition, two studies which reported more than one measure of exposure, showed conflicting results. In one case a trend was indicated while using the other measure, it was not. Only 10 of the studies showed any results which are

statistically significant at the 95 percent level, and for four of those studies, only the highest exposure levels yielded statistically significant results. Three of the latter group reported its results in terms of pack-years. One of that group, however, the study by Fontham did not show any statistically significant results when exposure was expressed in terms of smoker years.[42]

Table 5 - ETS Dose-Response Observations – (Smoker-Years)

Study	Exposure	RR	95% CI	Study	Exposure	RR	95% CI
18	1-21	1.6	(0.8,3.2)	6	1-19	2.1	(1.0,4.3)*
	22-39	1.4	(0.7,2.9)		20-39	1.5	(0.8,2.7)*
	≥40	2.4	(1.1,5.3)		≥40	1.3	(0.7,2.5)*
8	≤19	1.49	(1.15,1.94)	10	≤19	1.26	(0.56,2.87)
	20-39	2.23	(1.54,3.22)		20-39	1.62	(0.82,3.19)
	≥40	3.32	(2.11,5.22)		≥40	1.88	(0.82,4.33)
13	1-30	1.2	-	15	1-15	1.10	(0.83,1.46)
	≥31	2.0	-		16-30	1.33	(0.98,1.80)
					≥31	1.23	(0.91,1.66)
20	20-29	1.1	(0.7,1.8)				
	30-39	1.3	(0.8,2.1)				
	≥40	1.7	(1.0,2.9)				

Only eight of the studies which tested for trend found it to be statistically significant at the 95 percent level. Included in this group are two tier 4 studies;[43] without these studies, and with the 95 percent standard, only six would be significant. All of the trend analyses include zero exposure. If the trend was linear down to zero exposure, then including that level in the trend analysis would yield the same results as when excluded. If there was a threshold effect, then a trend test which included the zero exposure level might show a trend even if an analysis which included only exposures above zero did not show such a trend. In other words a sharp rise at some exposure level above zero could incorrectly be intrepreted as a dose response trend over all exposure levels.

As mentioned above, EPA calculated an overall relative risk from the relative risk values at the highest exposure levels even though these studies did not all use the same measure of exposure level. For the seven U.S. studies giving such information, a combined relative risk of 1.38 with a 90 percent

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[42] It should be noted that when reporting relative risk for non-smoking females against smoker years of exposure, Fontham included all sources of exposure at home while the results measured against pack-years included only spousal exposure.

[43] In assessing the utility of the various epi studies for evaluating a linkage between ETS and lung cancer, EPA established a ranking system of four tiers, the lowest of which is tier 4. Studies falling in tier 4 were excluded by EPA from its analysis of ETS and lung cancer.

confidence interval of (1.13,1.70) was calculated.[44] The EPA also performed a trend test for the combined U.S. studies and found it to be statistically significant at the 99 percent level.

It is also worth examining the reported risk values at the lower exposure levels. Based on the distribution of controls in these studies, a much higher fraction of the non-smoking population in the United States which is exposed to ETS, is exposed to the lower levels. Therefore, if there is a real effect at these lower levels, most of the risk would reside there. If there is a threshold exposure, however, it may be that most of the exposed non-smoking population would be at no risk from ETS. The studies reporting their results as function of cigarettes per day and smoker years which show a trend, give no indication of a threshold, i.e., a level below which the measured effect is negligible. For those studies presenting their results in terms of pack-years, however, all of them show negligible risks below some level, in the range of 40 pack-years. One study in this group showed no effect at any level.

ANALYSIS

Risk and Exposure Measurement

The results presented by these studies indicate that if there is any risk of developing lung cancer from exposure to ETS, it increases as the exposure level increases. As mentioned, however, both the size of the effects measured and the lack of consistent, statistically significant data lead to considerable uncertainty.

An additional problem in trying to extract any conclusions from these 20 studies is the different measures of exposure levels used, cigarettes per day, smoker years and pack-years. Pack-years -- an integrated exposure of daily intensity summed over time -- is probably a better way to measure exposure levels than cigarettes per day. This measure, however, is probably the least precise of the three measures because it is most subject to recall error. Evidence from studies linking direct smoking with lung cancer indicates that the risk increases in proportion to the number of years smoked at a given level. One might suspect that any lung cancer risk from ETS would behave similarly.

Only if there is perfect correlation between cigarettes per day and number of years of smoking would these measures serve as well as the pack-year measure. If that correlation is imperfect, the other dose measures are inferior to pack years, although the overall direction is likely to be the same.

At the same time, each of these measures require less recall. It is likely, however, that recall errors are more serious for number of cigarettes per day than for number of years, especially if smoking occurred in the past. That is, it is probably easier to remember how many years someone smoked than how much they smoked. If so, years might be the best measure of exposure if recall bias is severe.

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[44] EPA Report, p.144.

One implication of the potential disparity between the different types of exposure measurements is that combining risk assessments of several studies at the highest exposure levels probably yields misleading results.

All of the twelve studies using cigarettes per day as a measure of exposure show elevated risk at the highest exposure level although only about half are statistically significant -- not surprising given that most studies are small. Not all show a consistent trend, however. All four of the pack-year studies also show elevated risk at high exposures, with three out of four statistically significant. (Again, the largest studies show a statistically significant risk.) Of the six studies using years, all involve positive results but only two are identified as statistically significant.

The pack-year studies also offer evidence that non-smokers exposed to lower levels of ETS -- below 40 pack-years -- have little or no relative risk of developing lung cancer from ETS. The two largest case-control studies in terms of sample size -- Brownson and Fontham -- show this threshold behavior. Neither study, however, claims to be able to demonstrate a threshold effect because they lack the statistical power to make such precise measurements at such small levels of relative risk.[45] Indeed, as pointed out above, most epidemiologists state that it is virtually impossible to measure a relative risk below 1.1 using currently available epidemiology techniques. When considering the confidence intervals for the various exposure levels for these two studies, several different curves could be drawn, including a straight line, to represent the variation of relative risk as a function of exposure. Nevertheless, the possibility cannot be ruled out that a threshold level does exist if there is a real effect from ETS.

Confounding

Critics of studies which assert that ETS is associated with an increased risk of lung cancer claim that these studies have not adequately accounted for potential confounders. They argue that the small values of the relative risk found in these studies (usually less than 2) makes the probability relatively high that confounders are the cause. Potential confounders are behavioral patterns or biological conditions which may be a risk factor for the disease under investigation. To be an actual confounder, however, these patterns and/or conditions must be associated with the exposure under study in that study. This pattern and/or condition also must be present in sufficient strength to be a plausible source of the excess risk in the situation under study. A third test of a candidate confounder can be made using dose-response observations.[46] Any confounder that is to explain that risk likely would have to become stronger if and as the integrated ETS exposure increases.

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[45] Dr. Michael Alavanja, personal communication, June 12, 1995.

[46] Noel S. Weiss, , et.al., *American Journal of Epidemiology*, Vol. 113, No. 5, May 1981, p.487-490.

Critics argue that association of potential confounders with ETS exposure is likely to be met in ETS studies because the health habits of non-smoking spouses of smokers are similar to their smoking spouses and are, therefore, inferior to non-smoking spouses of non-smokers. Several studies have investigated this assertion. One group has examined the differences between exposed and unexposed non-smokers in terms of several dietary and related factors without attempting to measure relative risk, while the other group includes several studies which measured the relative risk of these factors in conjunction with that of ETS.

Two recent studies examined the dietary habits of a large populations of individuals who are exposed to ETS either at home or in the workplace.[47] [48] The two studies attempted to measure consumption of dietary nutrients suspected of being associated with cancer risk, often as an inhibitor to developing cancer. Neither study attempted to measure the differences in dietary behavior as a function of level of ETS exposure. Both studies showed a difference in diets between non-smokers exposed to ETS and those not exposed for most of the nutrients tested.

In one of the studies, however, only a few of the differences for the nutrients were statistically significant, and then only at the highest intake differences. The other study found that the differences investigated were all statistically significant, but that the dietary differences between exposed and unexposed non-smokers was much less than the corresponding differences between smokers and non-smokers. That study also concluded that the nutrient consumption by both exposed and unexposed non-smokers generally exceeded the recommended daily allowance. The authors speculated, however, that ETS and nutrients may interact in a way that would increase any nutrient requirements as a cancer inhibitor compared to when no ETS was present. The only disagreement between the two studies was dietary fat where Emmons, et.al., found that those exposed to ETS consumed a higher percentage of calories from fat than those unexposed, while Matanoski, et.al., found no difference in intake of fatty acids between the two classes of exposure.

In another study which investigated both the effect of ETS exposure and diet on lung cancer risk, only small differences were found between cases and controls for all foods included in the study except fruit.[49] The study found fruit intake generated a statistically significant relative risk for lung cancer of less than one; i.e., it acted as an inhibitor. Controlling for each of these factors showed them to be independent of one another in affecting lung cancer relative risk measurements.

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[47] Matanoski, et.al., *American Journal of Epidemiology*, Vol. 142, No.2

[48] Emmons, E.M.,, et.al., *European Journal of Clinical Nutrition*, Vol. 49, 1995, p.336-345.

[49] Kalandidi, A., et.al., *Cancer Causes and Controls*, Vol. 1, 1990, p.15-21.

A study focusing on beta carotene intake for non-smokers exposed to ETS compared to those not exposed found a statistically significantly lower amount in the former compared to the latter.[50] The authors estimated that such differences could act to reduce the measured relative risk -- total relative risk -- due to ETS by about 10 percent. No relationship between beta carotene intake and duration of exposure to ETS was found.

A 1991 study examined specific dietary habits of individuals exposed to ETS compared to those not exposed to ETS.[51] The study was confined to factors for which there has been evidence of an association with an increased risk of lung cancer, diets low in beta carotene, and high in cholesterol and total fat. Results showed an inverse correlation between ETS exposure levels and consumption of beta carotene, cholesterol and total fat among non-smokers. Exposure levels were measured by cotinine levels and, therefore, only measured current exposure. On the basis of risk values relating a low beta carotene diet to the risk of lung cancer, the researchers calculated corrections to the ETS risk values in order to determine the adjustment that may be needed because of reduced beta carotene consumption. He found corrections to the measured ETS risk values of about 11.5 to 12 percent. For cholesterol and total fat, however, since consumption decreased with increasing ETS exposure, any confounding correction would tend to raise the measured ETS risk value. No numerical corrections were presented in the paper.

Another study examined the possible contribution of a large number of food types as well as ETS to lung cancer risk among non-smoking women.[52] The study measured the relative risk of developing lung cancer as a function of the food dosage consumed. The only dietary components to have statistically significant relative risk factors were saturated fat, citrus fruits and juice, and beans and peas. The last food reduced the risk as its consumption increased. No effect due to beta carotene was observed. Furthermore, the authors reported that no interaction between ETS and the various dietary components could be measured. The most important contributor to increased lung cancer relative risk was saturated fat. Women who consumed the highest amounts of saturated fat -- a mean value of 20 percent of their daily calories -- had a lung cancer risk value of over 6. The paper reported that a biological link between saturated fat consumption and lung cancer was still speculative although preliminary experimental evidence of such a connection existed. The authors, however, were not able to offer any explanation for the connection between citrus fruit consumption and lung cancer risk.

Analysis of other potential confounders is not as extensive as for dietary factors but some work has been completed. One study explored the relationship

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[50] Sidney, S., et.al., *American Journal of Epidemiology*, Vol.129, No.6, June 1989, p.1305-1309.

[51] Loic Le Marchand, et.al., *Cancer Causes and Control*, Vol. 2, p.11-16.

[52] Alavanja, M.C.R., et.al., *Journal of the National Cancer Institute*,Vol.85,No.23, Dec.1, 1993,p.1906-1916.

between pre-existing lung disease (asthma, pneumonia, emphysema, bronchitis and tuberculosis) and lung cancer risk.[53] The authors measured a risk value of about 1.4 for never smoking women. From these results, the authors concluded that about 13 percent of all lung cancer deaths in never smoking women were due to a pre-existing lung disease. The research did not find any interaction between ETS exposure and pre-existing lung disease.

A 1983 study examined various factors including alcohol and marijuana consumption, and exposure to workplace hazards by a sample of the subscriber population at a Kaiser-Permanente Medical Care Center.[54] They found that these three factors were correlated with ETS exposure and, further, increased as exposure to ETS, as measured in hours per week, increased. The percentage of those exposed to ETS who also used alcohol and/or marijuana on a weekly basis was quite small, 7 percent or less, and included both males and females. The percentage exposed to workplace hazards ranged from 30 percent at no ETS exposure to 37 percent at the highest ETS exposure. The rate of increase in exposure to occupational hazards with ETS exposure reported in the study was modest. The number of survey participants who reported exposure to occupational hazards increased 7.5 percent as ETS exposure increased over 800 percent on average. The connection, if any, between rate of increase in exposure to occupational hazards and increased lung cancer risk was not given.

Finally, a study just published reviewed the lung cancer risk of a variety of potential confounders.[55] This paper reviewed interactions between the various suspected contributors to lung cancer in non-smoking women. The authors determined that about 48 percent of all those lung cancers could be explained by the seven factors they covered. The largest contributor measured in the study was saturated fat (22 percent) followed by former smoking (17.5 percent), pre-existing non-malignant lung disease (10 percent), ETS (6 percent), occupation (5 percent), family history of lung cancer (4 percent) and domestic radon (1.5 percent). All but the ETS and radon measurements were statistically significant. When only lifetime non-smokers were considered, however, the ETS contribution increased and became statistically significant. Among this group of non-smokers, ETS was measured to have accounted for 7.5 percent of all lung cancer deaths. This contribution was still exceeded by previous lung disease and saturated fat. In making these calculations, the authors controlled for all items except the particular factor being considered. No interactions between any of the items was found.

The evidence from these studies appears inconclusive about whether confounders may be responsible for the measured ETS risk values, particularly

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[53] Alavanja, M.C.R., et.al., *American Journal of Epidemiology*, Vol. 136. No.6, Sept. 15, 1992, p.623-632.

[54] Gary D. Friedman, et.al., *American Journal of Public Health*, Vol. 73, No. 4, April 1983, p.401-405.

[55] Alavanja, M.C.R., et.al., *Cancer Causes and Control*, Vol. 6, 1995, p.209.

those at the most extensive ETS exposure levels. While it is fairly clear there are differences between exposed and unexposed non smokers for many of these potential confounders, it is uncertain whether that difference will be of consequence in developing lung cancer. There are several reasons for this. First, with few exceptions the measured relative risks of these potential confounders are about the same as those measured for ETS exposure and are at least as uncertain as the ETS values. As a result, in order to account for much or all of the measured risk value, a confounder or combination of confounders would have to be present at levels intense enough to affect the etiology of lung cancer in many or all of the cases for which ETS induced lung cancer is suspected. Second, the potential confounder has to be either a likely cause or inhibitor of lung cancer. For example, alcohol consumption, which has been shown to be greater in exposed than unexposed non-smokers, and which is a suspected cause of some cancers, has not been shown to be connected by itself with lung cancer. There are indications, however, that excessive alcohol consumption in conjunction with smoking can increase the lung cancer risk.

Furthermore, the uncertainties exhibited in the measurements of the risk of most of the potential confounders, as expressed by the absence of statistical significance or conflicting results, suggests that none of them can be considered a clear cause or inhibitor. For example, there is considerable uncertainty about the role of beta carotene -- long thought to be a cancer inhibitor -- in affecting the risk of lung cancer. Beta carotene is often mentioned as a confounder because non smokers exposed to ETS appear to consume less than unexposed non-smokers. A recent study found that beta carotene not only did not inhibit the development of lung cancer, but may actually enhance the risk.[56]

A third reason is that there is disagreement, as reported above, about whether there are consumption differences between exposed and unexposed non-smokers for the potential confounder with the largest measured risk for lung cancer -- saturated fat. Fourth, studies which have attempted to control for these potential confounders -- in particular those by Fontham and Brownson -- do not find that they contribute any confounding to the measured ETS induced risk in those studies.

Fifth, evidence of potential confounders being correlated with increasing ETS exposure so as to offer a possible explanation for ETS dose response observations, is mixed. Examples of such confounder tracking has been reported, but for many of these confounders there is a question about whether they are a lung cancer risk factor. The cholesterol and total fat observations may mean that some confounders could raise the measured ETS risk values. Trend data showing the relationship between the levels of potential confounders and ETS exposure, are limited, however, so this possibility is speculative at this time.

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[56] The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, *New England Journal of Medicine*, Vol.330, No.15, April 14, 1994, p.1029-1035.

Misclassification Bias

Bias is generated from errors in the design, conduct, or analysis of an epidemiology study which result in a false measure of an association. There are several types of bias encountered in epi studies, including smoker misclassification, exposure misclassification and recall bias. Smoker misclassification would result from incorrectly assigning lifetime non smoker status to someone who actually smokes or who was a former smoker. Exposure, or random, misclassification would be the result of assigning someone to the exposed category when they actually had not been exposed to ETS. Recall bias occurs when someone reports an incorrect level of exposure to ETS because they are unable to recall the correct levels. Included is the situation of not recalling that one's spouse actually smoked. Some of these errors may be systematic in that they are a result of events or behavior which could be predicted to push the error in one direction. An example would be if some case group members provide incorrect information about their smoking or exposure status because of their disease status. Control group members, who do not have lung cancer, would have no reason to provide such incorrect information. Random errors cannot be predicted by events or behavior. Such errors are just as likely to occur in the case as control groups.

In this analysis, the consequences of each of the three types of misclassification will be examined using a mathematical model developed by EPA to calculate the downward correction to the observed relative risk values to account for smoker misclassification bias.[57] The model has been expanded to examine the effect of exposure misclassification and recall bias. In addition, modifications were made to allow for differential misclassification.

Smoker Misclassification

Smoker misclassification has drawn the most attention in the ETS studies to date. Surveys have indicated that a fraction of self-reported nonsmokers are actually current or former smokers. Because the relative risk of developing lung cancer from direct smoking is so high compared to any of the measured ETS risk values, it is possible that only a small percentage of smokers would need to be misclassified as nonsmokers to account for a large part of the measured ETS risk. Furthermore, while such misrepresentation can occur for both exposed and unexposed non-smokers (both cases and controls), it may be more likely to occur to the former because smokers tend to be married to smokers. This situation would create a bias resulting in an overestimation of the risk value because it would increase disproportionally the observations in the exposed cases.

The EPA model used to assess the consequences of smoker misclassification is dependent on a number of parameters including the misclassification rates of current regular female smokers (although they may have just recently quit), former female smokers, occasional female smokers, and the risk of developing

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[57] EPA Report, p.311-335.

lung cancer from smoking for each group.[58] In addition, the prevalence rate of never smokers for the group under study is required. There are several other parameters needed for the model which must be derived from experimental observations, but those listed above are the most critical.

Table 6 - Smoker Misclassification Consequences

Misclassification Condition	Required Rates and Adjusted RR Values	
	Rate -% (RR=1.0)	Rate-% (CI≤1.0)
Non-differential	10.1	2.8

To see the consequences of smoker misclassification, the model is used to calculate the misclassification rate of current (or recently quit) female smokers that would be needed to reduce a measured ETS risk value to 1.0.[59] A second test is to determine the current smoker misclassification rate needed to cause the measured risk to no longer be statistically significant at the 95 percent level. For this test, the model is used to find the rate when the lower limit of the 95 percent confidence interval drops below 1.0. The results are shown in table 6. The Fontham study is used for this analysis because it provides most of the data needed for the model and the rest of the data is available from the EPA study.[60] The calculations are carried out on the measured risk value at the highest exposure level, 79.9 pack-years or more. For example, if the smoker misclassification rate were 10.1 percent, the measured risk of 1.87 for that exposure group would actually be 1.0, indicating no risk from ETS. All of the measured risk would be due to a group of smokers who had been incorrectly identified as non-smokers.

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[58] The most common method of determining smoker misclassification is through measurements of cotinine levels in the blood. Because of the time sensitivity of this measurement, it will not pick up individuals who have recently quit (within a several month period prior to the measurement). Such people still retain the high risk associated with smoking, however, and should be included in any complete accounting of the current smoker misclassification rate.

[59] The EPA model assumes that the former smokers have not been smoking for at least 10 years. This condition led EPA to use a value for excess risk for former smokers which was about 9 percent of the value of the excess risk of current smokers. This assumption results in a total relative risk for those in the former smoker category only slightly higher than measured values of ETS relative risk. Therefore, smokers who had quit more recently and had a higher excess risk, must be included in the current smokers category. For occasional smokers, EPA assumes that their relative risk is 16 percent of that of current smokers based on cotinine measurements which showed levels of cotinine in occasional smokers to be on average 16 percent of that of current smokers.

[60] EPA Report, p.327. It is important to note that Fontham undertook extensive efforts to minimize the effect of smoker misclassification (see below). The use of the Fontham data for these misclassification rate calculations does not imply that such rates are necessarily likely for their study.

To simplify the analysis, misclassification rates for long ago former smokers and occasional smokers are arbitrarily set to zero.[61] The result of this analysis is shown in table 6 above for the case of non-differential misclassification (equal rates in both the control and case populations), the standard assumption made in smoker misclassification corrections.

Exposure Misclassification

Next, the model is used to examine the consequences of exposure misclassification. When a case and/or control group member identifies herself as having a smoking spouse but is actually unexposed to ETS, the participant is incorrectly counted as exposed. Adjusting for such exposure misclassification would increase the measured relative risk. Table 7 shows the effect of this misclassification on the measured values of risk as a function of exposure level for the Fontham study. Two misclassification rates are chosen for illustration -- 10 percent and 20 percent. For example, at the highest exposure level -- above 80 pack years -- if 10 percent of those cases or controls who state their spouses smoke actually are not exposed to ETS, the measured risk rate of 1.87 would actually be 1.89. If that exposure misclassification rate were 20 percent, the actual risk would be 1.90. No studies have been done to date attempting to measure exposure misclassification rates. In order to carry out this illustrative calculation, it has been assumed that the misclassification rate is the same for both controls and cases. Further, the misclassified individuals were distributed among the various exposure levels in proportion to the number of cases and controls in that level.

Table 7 - Relative Risk -- Exposure Misclassification

Exposure Level (pack-years)	Misclassification		
	0	10%	20%
≤15.0	1.02	1.04	1.06
15.1-39.9	1.02	1.03	1.05
40.0-79.9	1.34	1.35	1.38
≥80.0	1.87	1.89	1.90
All Levels	1.12	1.13	1.15

Recall Bias

Recall bias is simulated in the model by assuming that a fraction of the exposed members of the case and control groups have either overestimated or underestimated their exposure level. To see the effect of recall bias, a few illustrations are presented. The data from the Fontham paper are used for

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[61] Including them at levels used in the EPA analysis (11.7 percent for long ago, former smokers and 24.2 percent for occasional smokers) and with the same assumed lung cancer risk rates used would result in a decrease -- about 20 percent -- in the regular smoker misclassification rates needed to drive the relative risk to zero or to make the measured risk no longer statistically significant at the 95 percent level. If either or both of the relative risk values for occasional and long ago former smokers is increased above those assumed by EPA, the contributions of these two categories to smoker misclassification bias will grow.

these illustrative cases.[62] First, recall bias rates are calculated which would be required to reduce the relative risk for each exposure level to the average relative risk for all levels; i.e., to eliminate the dose response trend. In this first illustration, it is assumed that only the cases are subject to recall bias. The effect of recall bias in the controls will be discussed below. For the data being used -- Table 3 in the Fontham paper -- the average relative risk is 1.12. The results, shown in table 8, give the required recall bias rates for each level to reach that value. A positive rate means that some participants at that level overestimated their exposure levels and actually belong at lower exposure levels. Negative values indicate how much these exposure levels should grow in order to flatten the dose-response curve. For example, at the highest exposure level -- above 80 pack-years -- if 40.1 percent of the case members in that group had over estimated their exposure and it actually ranged between 40 to 79.9 pack-years, the actual risk of the above 80 pack year group would drop to 1.12 from the measured value of 1.87. For the exposure level below 15 pack-years, if 9.3 percent had underestimated their exposure and actually belong in the next highest group -- 15.1 to 39.9 pack-years -- the actual risk for the lowest exposure level would rise to 1.12 from the measured value of 1.02. The final column gives the net number of people shifted to each level corresponding to the recall bias rate. A negative number, of course, means that participants are lost from that level. None of the adjusted relative risk values are statistically significant.

Table 8 - Effects of Recall Bias

Exposure Level	RR	Bias Rate(%)	Adj RR	Cases Shifted
≤15.0	1.02	-9.3	1.12	14
15.1-39.9	1.02	-10.0	1.12	9
40.0-79.9	1.34	16.2	1.12	-13
≥80.0	1.87	40.1	1.12	-10

Another indication of the effect of recall bias can be seen by calculating the change in smoker misclassification rate needed to push the relative risk at the highest exposure level -- 80 pack-years and above -- to 1.0 (no risk) for a given recall bias rate. Again, Fontham data were used. For a recall bias rate of 0, a smoker misclassification rate is 10.1 percent would be required to cause this reduction. If the recall bias rate at the highest exposure level increases to 10 percent, the smoker misclassification rate required for the actual risk to be 1.0 drops to 9.4 percent. A third test shows that with a smoker misclassification rate of zero, a recall bias rate of 4.5 percent in the highest exposure level will push the lower limit of the 95 percent confidence interval to below 1.0. These calculations were all done assuming an exposure misclassification rate of zero.

While a recall bias which overestimates ETS exposure in the cases reduces the upper level relative risk, the same type of recall bias in controls would raise

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[62] Fontham, et.al., p.1754.

it. With no smoker or exposure misclassification, a 10 percent recall bias rate in the controls would cause the relative risk value to increase from 1.87 to 2.08. Finally, if the recall bias in the cases is in the other direction -- i.e., non-smokers underestimate their ETS exposure, the effect is to raise the relative risk. A 10 percent recall bias in the highest level of exposed cases would increase the relative risk from 1.87 to 2.06. Of course, a similar type of recall bias in the controls would act to lower the relative risk.

Discussion

The calculations presented above are just a sample of the very large number of misclassification rate combinations possible in these ETS studies. It seems clear from those results, however, that possible combinations of small rates -- below 10 percent -- could drive ETS relative risks in the highest exposure groups to values no longer distinct from 1.0, even in a study that produces relatively high risks. While these results were obtained from the Fontham study, similar results are likely from the Brownson study.[63] Even smaller values of these rates -- below 3 percent -- could be combined to reduce the lower bounds of the 95 percent confidence intervals well below 1.0 for these studies. On the other hand, it appears possible to construct combinations of relatively small misclassification rates -- again less than 10 percent -- which would increase the measured relative risk. The major problem with assessing the likelihood of any of these paths is the absence of data. While there exist some spotty data on smoker misclassification, there is very little information to provide guidance about values for the other two rates -- exposure misclassification and recall bias. The rest of this discussion focuses on each of the three error rates.

Smoker Misclassification - Discussion.

Few studies have been done to measure smoker misclassification rates results to date. EPA used a rate of 1.09 percent for current smokers which was determined by measuring cotinine levels in self-reported female non-smokers. There has been criticism of its choice of that value.[64] More recent unpublished results by Roger Jenkins of the Oak Ridge National Laboratory indicate that the rate may range from 2.5 to 4.6 percent depending on how one classifies former or current smokers according to chemical markers.[65] Given the potential influence of former smokers (not accounted for in this illustration), whose cancer risk could be higher than that assumed by the EPA, and the sampling variability of misclassified smokers in different samples, smoker misclassification

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[63] Brownson, et.al., p.1528. A complete set of parameters necessary for carrying out these calculations is lacking for the Brownson, et.al., study. It is unlikely, however, that those parameters will differ sufficiently from the Fontham, et.al., case to change this conclusion.

[64] Dr. Maxwell W. Layard, personal communication.

[65] Roger A. Jenkins, *Addendum to comments on Proposed Rulemaking Occupational Safety and Health Administration 29CFR parts 1910,1915,1926, and 1928 Indoor Air Quality; Proposed Rule*, Oak Ridge National Laboratory, December 22, 1994, p.30.

could explain all the measured risk even at high exposure levels even for studies such as Fontham and Brownson.

A major question about smoker misclassification is the degree to which an investigator would be able to find out whether a case -- or control -- participant is actually a non-smoker. The probability that the truth could be determined seems good but not certain. It is difficult to believe that the medical records of a smoker who developed lung cancer would not indicate that person's smoking status. The records may not have been complete or accurate in all cases, however, and, for various reasons, the records were not always reviewed. The Fontham study, for example, made a substantial effort to control for this factor. For example, it used cotinine screening to test participants and eliminate them from the study if the concentrations exceed a pre-determined threshold. It also used extensive follow-up questionaires and physician interviews to check on the smoking status of the case and control members. The cotinine screening, of course, will only determine current smokers. Smokers who quit upon developing lung cancer and then denied that they ever smoked when answering the questionnaire would not be discovered by this screening. Also, the follow-up questionaires and interviews are still subject to incomplete or false information.

There is also an issue as to the incidence of former smokers reporting themselves as non smokers. The only studies that exist currently are those which identify the rate based on discordant answers -- instances where different answers were given on different questionnaires, and these data are limited. That evidence, although skimpy and mixed, led to a misclassification rate of 11.7 percent. There is no information on individuals who consistently misrepresent their former smoking status.[66] Although this misclassification rate was high relative to the current smoker rate, it did not loom very large in the EPA adjustment because they also assigned a very low cancer risk rate to former smoking, under the assumption that these were long term ex-smokers. But, if the cancer risk rate is larger (because these individuals quit in the past few years) or if there is more misclassification, these effects could be much larger.

Another issue is whether the smoker misclassification rate could be differential, i.e., higher for either cases or controls. In the non-differential situation, the misclassification rates for cases and controls are equal. Because the relative risk for lung cancer from smoking is so much greater than any of the estimates from ETS, however, the effective rate for cases would be much greater than for controls because the former is weighted by the smoker lung cancer risk value. If the misclassification rate for controls was greater than that for cases, part or all of this weighting would be offset depending on the size of the differential. The difference would have to be substantial, however, to offset the downward correction. If the rate was higher for the cases, the necessary rate to reduce the measured relative risk to 1.0 would drop. Little data exist about non-differential misclassification. In the Fontham study, cotinine

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[66] A possible reason for such misrepresentation relates to life insurance policies which differentiate premiums. In some instances such policy can become null regardless of what the individual died from if he lied on his application.

measurements to eliminate possible smokers did find a higher rate among the controls than the cases.[67] Because of the limitations of cotinine as a means of determining smoker misclassification, this result may not be indicative of any differential smoker misclassification more generally. For instance, if lung cancer victims quit smoking upon diagnosis and denied ever smoking, they could be misclassified as non-smokers but would not be discovered by cotinine methods.

The test to determine the number of case group members that would need to be misclassified from current to never smokers in order for the calculated risk value to lose its statistical significance in the above illustration, shows much lower misclassification rates. For the Fontham data, a non-differential rate of less than 3 percent would cause the measured risk value at the highest exposure levels -- 80 pack-years or more -- to lose its statistical significance. The implication of this result is that misclassification rates well within those measured could render all measured ETS risk values no longer statistically significant. Whether that is sufficient to conclude there is no lung cancer risk from ETS depends on how one interprets statistical significance as discussed earlier in this report.

Exposure Misclassification - Discussion.

The results of the simulation show that exposure misclassification has little effect on the measured relative risk. For misclassification rates up to 20 percent, the actual risk value would increase by 4 percent or less from the measured value in all examples considered. One source of exposure misclassification is those cases and controls whose spouse smoked, but did not do so in the presence of the non-smoking spouse. This situation is likely to be confined to the lowest exposure categories since it would seem very difficult to avoid exposure in those cases where the spouse smoked heavily. Accounting for this possibility in the model shows less than a percent change in the corrected relative risks. It is also interesting to note that the inclusion of exposure misclassification actually reduces the smoker misclassification rates needed to drive the highest exposure relative risk to 1.0 or to reduce the lower bound of the 95 percent confidence interval below 1.0, although the changes are small. Since correcting for exposure misclassification removes cases and controls from the exposed category, apparently a smaller percentage of misclassified smokers would be needed in that category to account for the measured risk.

Actual measurements of exposure misclassification appear to be beyond current study techniques because of the detailed recall which would be required by the cases and controls. Measurements of non-smoker's exposure to ETS using monitors has been attempted (see section on exposure), but these measurements are only feasible over short periods, and no attempt has been made so far to look at the variation in actual exposure for similar levels of spousal smoking. In any event, the corrections are quite small and do little to account for the uncertainties associated with ETS and lung cancer risk.

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[67] Fontham, et.al.,p.1757.

Recall Bias -- Discussion.

Simulations of recall bias show substantial rates would be necessary, by themselves, in order to reduce the highest measured relative risk values to those essentially no different than 1.0 for the Fontham study. The direction of the simulated bias is for those at the highest exposures to overestimate their exposure by enough to put them into a lower exposure level. The same effects could occur if controls underestimated their exposure on average. Such a differential might simply occur because cases are more focused on exposure due to their disease status and provide more accurate answers, while casual answers to exposure questions by controls tend to recollect less exposure than actually occurred. Much lower rates of recall error, of course, would be needed to render relative risk values no longer statistically significant.

While there are no direct data available about recall bias rates, there are data which might be used to evaluate the likelihood of the recall bias. One study examined reliability of responses to questionnaires about exposure to ETS by repeating the questionnaire six months after first given.[68] The authors found that reliability was quite high in terms of whether the participants were exposed, but much lower about the level of that exposure. The results indicated that second interviews reported lower duration of exposure and that reliability of reporting duration was poor. A second study done on smokers compared recall of their smoking habits with information obtained on their smoking behavior six years prior.[69] The results showed that those whose smoking habits did not change had high recall accuracy while those whose smoking had increased tended to overestimate the amount they smoked and those whose smoking had decreased tended to underestimate the amount they smoked. In other words, recall was biased towards their current habit.

These studies indicate that recall bias is prevalent and may be at a relatively high rate. The two studies do not, however, indicate which direction the biases may flow. The reliability analysis was not able to determine which of the two values of exposure duration was correct. And in order to apply the results of the retrospective study, it would be necessary to determine how the current smoking habits of the smoking spouse had changed over time. Even then, these results might not hold for the cases where recall was not based on the recollection of the smoker, but rather the spouse or some surrogate.

One could speculate that cases might more accurately recall spousal smoking behavior simply because their thoughts are more likely to be focused on the causes of their disease, but such a speculation has not been tested empirically. There is some evidence, however, that recall bias may exist in a way that biases the results towards more effects at high levels because of the

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[68] Pron, G.E., et.al., *American Journal of Epidemiology*, Vol.127.No.2, 1988, p.267-273.

[69] Persson, P., et.al., *American Journal of Epidemiology*, Vol.130,No.4, 1989, p.705-712.

overall incidence of negative risks in the lower exposure categories.[70] If such is the case, then results such as those in Brownson (with no overall effect, a negative risk at low exposures, and a positive one at high exposures) could be a result of recall bias. Of course, there may be a subjective tendency towards exaggeration or denial on the part of cases as compared to controls as well.

Another recall issue relates to study metholodogy. Several investigators have examined whether the pattern of association between ETS exposure and lung cancer depends on the type of interview conducted. When the case was too ill to be interviewed or deceased, exposure information was obtained from a surrogate such as the case's husband or one of her children. In epidemiologic research, surrogate interview data are usually presumed to differ in quality from interview data obtained directly from the subject. However, in spousal ETS studies, the husband may provide more reliable information about his smoking habits than his wife.

Janerich et al. conducted almost one-third of their case interviews with surrogates and found that these data produced markedly lower risk estimates than the information obtained from direct interviews. This suggests that surrogates may have underestimated spousal exposure. The study did not indicate what proportion of the surrogates were husbands.

Only 12 percent of the cases were interviewed directly in the Garfinkel et al. study. Of the surrogate interviews, 29 percent were conducted with husbands and the remainder were with daughters, sons, or close friends. Interviews with children produced considerably higher overall risk estimates (RR=3.19) than did the direct interviews (RR=1.0) or those conducted with husbands (RR=0.92). These results may be due to the fact that the children of the cases overestimated the exposures that their mothers received from their fathers' smoking. It is also possible, though perhaps less likely, that cases and their husbands may have underestimated the exposure.

Stockwell found the opposite effect in their analysis of direct and surrogate interviews. Two-thirds of the interviews were conducted with surrogates, a third of which were with the husband. Risk estimates based on interviews with the case and her husband produced similarly elevated estimates of overall risk (RR=3.1), whereas risk estimates based on other surrogate respondents, primarily children, were considerably lower (RR=0.9).

Brownson also relied on surrogates for about two-thirds of the case interviews, though only about a quarter of these were with the case's husband.

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[70] Maxwell Layard, personal communication. Layard carried out a meta-analysis on several studies giving dose response data. He showed calculated a relative risk value of 1.28 with a 95 % confidence interval of (1.07,1.52) when combining results at the highest exposure levels of each of the studies and a relative risk value of 0.91 with a 95% confidence interval of (0.79,1.06) at the studies' lowest exposure levels. These studies, however, used different measures of exposure -- smoke-years, cigarettes per day and pack-years -- so combining their results may yield misleading results.

Butler analyzed Brownson's data and found that the reported increase in risk associated with at least 40 pack-years of exposure occurred only among those with a surrogate interview.[71] There was no clear pattern of increase or decrease in risk estimates when the analysis was limited to direct interviews.

These studies suggest that the use of surrogate interviews introduces an additional, and potentially significant, source of recall bias. However, there is no consistent pattern in the direction and magnitude of this bias. An analysis of other ETS epi studies that included both direct and surrogate interviews may shed light on this type of bias.

Final Comments

It is clear that misclassification and recall bias plague ETS epidemiology studies. It is also clear from the simulations that modest, possible misclassification and recall bias rates can change the measured relative risk results, possibly in dramatic ways. Aside from smoking misclassification, however, attempts to correct for them have not taken place because there is currently no information available on how to carry out such corrections. It is possible that more research on the general question of misclassification will reduce the uncertainty now present in these ETS results, but such research will be difficult to perform because its methods, too, appear to be subject to considerable uncertainty.

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[71] Butler, W.J. Lung Cancer and Exposure to ETS in the Household and in the Workplace: Additional Analyses of the Data from a Negative Study, Brownson et al. (1992). Submitted to OSHA Docket H-122, September, 1995.

ETS AND LUNG CANCER DEATH RISK

INTRODUCTION

The magnitude of the potential risk from lung cancer death from ETS is not readily determined directly from the results of the epidemiologic studies (except, of course, in those studies where no risk is estimated). For example, the finding in the recent Fontham study that there is an overall risk of 29 percent can be misleading when expressed by itself. Since lung cancer is a rare disease among nonsmokers, even a doubling of the risk would be a small risk compared, say, to the risk of lung cancer among smokers, or the risk of many other diseases and accidents. Moreover, because of sampling variability, the risk found in these studies is more appropriately represented by a range of risks. Finally, the interpretation of risk from these studies is influenced by whether the assumption is made of a zero threshold (any ETS exposure causes some deaths) or a threshold that is higher (a certain level of ETS exposure is required to cause deaths).

This chapter examines the risk of lung cancer death from ETS from these perspectives. The Fontham study, which provides adequate data for illustrating these effects, is used to demonstrate the range of estimates, incorporating statistical uncertainty and different threshold assumptions. An earlier version of this study was the basis of some of the EPA estimates (along with an estimate from the overall findings of the 11 U.S. studies) in the neighborhood of about 3000 deaths with a no-threshold assumption. That calculation is performed using the methodology developed by EPA and the National Research Council (NRC). The purpose of the section is not to compute a definitive number of lung cancer deaths which may result from ETS, but rather to illustrate the effect of various factors -- e.g., confidence intervals -- on those numbers. For example, using the Brownson study, which is also a large U.S. study, would have produced dramatically different results -- in particular, this study would produce no deaths from ETS with a no-threshold model. The second section of this chapter uses those estimates to compare risks arising from ETS to other risks.

METHODS

Population Attributable Risk

The approach used by EPA and the NRC is to calculate the number of lung cancer deaths for non-smokers resulting from exposure to ETS from the relative risk measurements determined from the epi studies.[72] First, measured values of the relative risk for non-smokers developing lung cancer as a result of exposure to ETS from spousal smoking are adjusted to account for exposure to background ETS. The adjusted relative risks are then manipulated to determine a population-attributable risk (PAR). The PAR is the fraction of lung cancer deaths of non-smokers that is due to a given risk factor, or exposure type. The

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[72] For details of these calculations see EPA report, pg. 173-201; and National Research Council report, pg. 289-293.

PAR for each type of exposure -- background alone, and spousal and background combined -- is multiplied by the number of lung cancer deaths of non-smokers in a given year to estimate the total number of these deaths due to the exposure type. Since the epi studies involve only women, the PARs are used to calculate the number of ETS lung cancer deaths for non-smoking females only. Other methods, based on these results, are used to calculate the lung cancer deaths for non-smoking men and former smokers who quit long ago.

Background ETS

Both the NRC and EPA proposed that the relative risk values measured by the epi studies were understated because all participants in the studies, whether or not exposed to ETS, were also exposed to background ETS. Risk due to spousal exposure is measured in these studies by comparing the ratio of cancer cases to controls in the exposed group (women married to smokers) to the ratio of cancer cases to controls in the unexposed group (women married to nonsmokers). The extra cancer cases that drive the former ratio up relative to the latter are attributed to spousal exposure. But if both groups are exposed to background ETS, there are other cancer cases in both the spousally exposed and unexposed that arise from background exposure. Therefore, the relative risk values directly measured by the epi studies were lower than they would be if they were determined relative to a "truly" unexposed group.

Both the NRC and EPA compared cotinine levels in non-smokers exposed to spousal ETS to those in non-smokers who declare they have not been exposed to spousal ETS. The cotinine measures are then used to calculate relative exposure levels and estimate deaths resulting from background exposure both for nonsmoking women married to smokers and those not married to smokers. This estimate requires information on the share of non-smoking women married to smokers, which is generally available from the studies. This method requires the following assumptions: first, a linear relationship exists between cotinine levels in non-smokers and amount of ETS exposure; second, the level of cotinine measured in a given non-smoker does not change over time (i.e., exposure to ETS is constant); and third, there is a linear relationship between the dose of ETS to which a non-smoker is exposed and the excess risk of lung cancer.

The EPA extended the calculations of lung cancer deaths attributable to ETS to male non-smokers and former smokers -- both female and male -- who quit long ago. The latter category is defined as those males and females who have not been smoking for a period of five years or more.

According to the EPA, there are no reliable studies which determine the relative risk of lung cancer for non-smoking males as a result of exposure to spousal ETS. In order to make an estimate of ETS based lung cancer deaths for this group, therefore, the EPA assumed that the lung cancer mortality rates (LCMR) determined for female non-smokers would be the same for male non-smokers, and for all long ago, former smokers. The LCMR for female non-smokers as a result of background ETS alone is determined from the ratio of the number of cancer deaths from background ETS for this group to the total

population of female non-smokers. The LCMR for female non-smokers as a result of both spousal and background ETS is determined from the ratio of the number of cancer deaths from exposure to both kinds of ETS to the total population of female non-smokers exposed to both types of ETS.

To complete the calculation of lung cancer deaths attributable to ETS, estimates are needed of the population of each group -- male non-smokers and all long ago, former smokers, and estimates of the shares of these individuals exposed to spousal ETS.

RESULTS

Exposure Patterns

The methodology and its approach to measuring background exposure described above reflects a zero-threshold model, which assumed that even light exposures to ETS result in some risk. This model also permits the measurement of risk for two different categories of the population: those exposed to spousal along with background and those exposed only to background. An alternative model is one that is based on a threshold. The Fontham and Brownson results provide some indication of the possibility of a threshold.

Two issues are important in this analysis. First, if the risk is concentrated among non-smokers at the high end of the ETS exposure range, the percentage of any group of non-smokers which may be at most risk may be relatively small. A second issue is the range of possible lung cancer deaths for a given mean relative risk. The 95 percent confidence intervals around the mean value give an indication of this range. The values of lung cancer deaths at each end of the range would give a clearer picture of the uncertainty inherent in the measurements.

In order to analyze these issues, two illustrative sets of calculations are made. The first set illustrates the range of deaths possible by calculating the number of lung cancer deaths from the non-smoking population for the mean value of the measured relative risk, and for the upper and lower bounds of the 95 percent confidence interval. For these calculations, the no-threshold approach, as performed by EPA, is used. The second set illustrates the effect of a dose-response relationship on the number and distribution of lung cancer deaths in the non-smoking population exposed to ETS. To do this, a calculation is performed which compares both no-threshold and threshold exposure situations. The threshold situation assumes that only a portion of non-smokers -- subjected to the highest ETS exposure levels -- has an ETS lung cancer relative risk greater than one. This calculation should bracket any more realistic dose response relationship. Because of the availability of the data to do both of these sets, the results of the Fontham study are used to make these calculations. Results from other studies as well as the EPA results will also be discussed where appropriate.

It is important to point out that the threshold illustration is a hypothetical example and does not mean that any lung cancer which might result from ETS exposure would actually exhibit a threshold dose response relationship. While data from some studies have shown such behavior as seen in the previous chapter, the statistical power of those studies is too weak to conclude that such a behavior exists.[73] The use of a threshold model in these calculations is only to simulate the upper limit of a possible upward dose response behavior in order to bracket the range of consequences of possible dose response relationships. Finally, even if a threshold model were approximately correct, public health officials may still chose to use a model closer to the no-threshold approach in order to build in ensure that all populations are protected.[74]

Background Exposure

As described above, the measured relative risk values must first be adjusted for background exposure. The cotinine measurements (discussed above) allow determination of a factor, Z, which is the ratio of total exposure (spousal plus background) to background exposure alone. For instance, a Z value of 2 would mean that a typical member of the group exposed to spousal and background ETS would be subjected to twice the total ETS exposure as a typical member of the background only group. Once the Z value is determined, the NRC methodology is used to calculate the adjusted risk values. The higher the Z value, the lower the effect of background ETS on the risk of lung cancer death.

Lung Cancer Deaths

Results of the illustrative calculations are presented in the two tables on the following pages. In table 9, the first illustration shows the results for average relative risk applied to the entire non-smoking population at risk (This approach, which is the same as that followed by the NRC, hereafter is called the no-threshold risk approach.) and is calculated from a mean value of relative risk of 1.29 from the Fontham study.[75] The second and third illustrations give results under the same conditions but using the upper and lower limits of the 95% confidence interval of 1.60 and 1.04 respectively. In all cases, Z = 2.6.[76] This Z value means that total exposure is 2.6 times as high as background exposure alone as determined by cotinine measurements. The subscript "x" indicates exposure to both spousal and background ETS while the subscript "o"

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[73] In Brownson, et.al., (1995), the authors calculate the population risk of ETS exposure relative to an exposure level of 40 pack-years. While they do not claim this action implies a threshold condition to exist, the effect is similar.

[74] Steve Bayard, personal communication.

[75] In the Fontham et.al. study, the authors measured an adjusted relative risk of 1.29 with a 95% confidence interval of (1.04-1.54) for non-smoking women exposed to spousal ETS from all types of tobacco.

[76] EPA report, p.193.

Table 9 -- ETS Lung Cancer Death Estimates (average (uniform) exposure)					
Exposure Type	Population (Millions)	% at Risk	Pop at Risk (Millions)	LCD	LCMR (per Million)
Illustration I - Uniform Risk: RR = 1.29 (mean value)					
$(F + M)_x$	32.3	100	32.3	2085	64.5
$(F + M)_o$	36.8	100	36.8	710	19.3
Totals	69.1	100	69.1	2795	40.4
Illustration II - Uniform Risk: RR = 1.60 (upper 95% CI value)					
$(F + M)_x$	32.3	100	32.3	4415	136.7
$(F + M)_o$	36.8	100	36.8	1070	29.0
Totals	69.1	100	69.1	5485	79.4
Illustration III - Uniform Risk: RR = 1.04 (lower 95% CI value)					
$(F + M)_x$	32.3	100	32.3	340	10.5
$(F + M)_o$	36.8	100	36.8	130	3.5
Totals	69.1	100	69.1	470	6.8

refers to background ETS only.

In the table, LCD means lung cancer deaths, LCMR means lung cancer mortality rate (per one million population at risk), RR means relative risk, and CI means confidence interval.

In order to consider the threshold results, it is necessary to examine a subset of the Fontham data that classified exposure by pack years.[77] That subset has a lower overall risk (1.12 rather than 1.29) arising partly from the elimination of pipe and cigar exposure, and partly from missing cigarette smoke exposures that did not answer the question. (Neither the cigarette exposure nor this subset is statistically significant, so that this comparison will not include confidence intervals). Those results show a sharp increase in the relative risk at about 40 pack-years of ETS exposure.

The no-threshold simulation uses the mean value of the relative risk from these data for all exposed non-smoking females of 1.12. Otherwise, it uses the same methodology as the estimates in table 1. The results are a total of 1270

[77] Fontham, et.al.,Table 3,p.1754.

deaths, with 915 due to those who are exposed to spousal as well as background, and 355 due to those who are exposed to background alone.

The threshold simulation, using the Fontham data, assumes a relative risk of 1.0 for all non-smoking females subjected to less than 40 pack-years and the mean value of 1.43 for all above 40 pack-years. Background risk plays a different role in this threshold case. Recall that in the no-threshold case, risk due to spousal smoking is determined by comparing the incidence of cases in the exposed vs. the unexposed group. But, since background exposure is common to both groups, the incidence of cases would be equal in the two groups even though some are due to background exposure. In the threshold case, exposures are divided into three or more groups, and the data would show no risk for the low spousal exposure case(s). A certain level of exposure is required to cause risk. Even if the level of spousal exposure alone is not enough to exceed the threshold, the combination of spousal and background together would be greater in the lower exposed spousal groups than in the groups not exposed to spousal. The fact that no risk is found in the low spousal exposure case indicates that there is not enough exposure of any kind to induce effects. The role played by background exposure is to push up the risk ratio in the highly exposed group by pushing more individuals in that group over the threshold. In this case, however, the risk estimated directly from the study is the total risk as it has already been influenced by background exposure.

The dose response relationships for all male non-smokers and all long ago, former smokers exposed to spousal ETS and for those exposed only to background ETS is assumed to match the patterns of their female counterparts.

In this threshold case, the number of estimated deaths is 440, or only 35 percent of the no-threshold case. This calculation demonstrates how significantly risk estimates can be reduced in a threshold model, primarily because there are no additional lung cancer deaths resulting from background exposure. In the EPA's risk estimates about 70 percent of total risk was not directly estimated from the epi studies but rather was attributed to background exposure. Background smoke still contributes to risk in the threshold model -- if all background exposure disappeared the risk would presumably fall, but there is no risk among those subject only to background exposure since they are all below the threshold. A rough calculation shows that if equal background exposure is assumed for all, about 30 percent of deaths in the threshold model would be eliminated if background exposures were eliminated; at the same time, 100 percent would be eliminated if spousal exposure were eliminated.[78]

Note that in all of these calculations, data on the populations of different groups of male and female non-smokers and former smokers, and the total number of lung cancer deaths for female non-smokers are obtained from the

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[78] This calculation is based on estimating an average background exposure relative to the high exposure, based on average pack years in the different groups. The same Z value is used for the overall population, but a higher one, about 6.2, for the ratio of heavy spousal exposure to background exposure.

EPA study.[79] Data on the percentage of all female non-smokers exposed to spousal ETS are obtained using control population data from the Fontham study.[80]

DISCUSSION

For the illustrations based on the no-threshold risk for the entire non-smoking population, the number of lung cancer deaths estimated from the Fontham study relative risk measurements, ranges from 470 to about 5500 with a mean value around 2800. For the entire non-smoking population at risk -- estimated to be about 69 million in 1985 -- these numbers translate into a death rate ranging from about 7 to 80 per million with a mean value of about 40 per million. By way of comparison, EPA estimated about 3000 deaths from ETS exposure for a death rate of about 43 per million. The estimated death rates vary substantially depending whether one is exposed to spousal ETS or not. In the former case, from the Fontham data, the rates range from 10 to 136 deaths per million exposed. For those unexposed to spousal ETS but exposed to background ETS, the rates range from 3.5 to 29 deaths per million.

Turning to the comparison of the no-threshold and threshold dose-response conditions, the no-threshold example yields a total of 1270 lung cancer deaths while the threshold example yields about 440. In the latter instance, the percentage of the population at risk drops to about 13 percent of the entirepopulation of non-smokers, all of which are from the spousally exposed group.

The actual dose-response pattern is not likely to exhibit a true threshold, nor is it likely to be flat or even linear. As argued in the previous chapter, while the epi measurements contain considerable uncertainty, there is evidence pointing towards some type of dose response relationship. Therefore, if there are any lung cancer deaths from ETS exposure, they are likely to be concentrated among those subjected to the greatest, integrated exposure levels, and, as a consequence, primarily among those non-smokers subjected to significant spousal ETS.

The potential contribution of background ETS to lung cancer deaths is another source of uncertainty. In the no-threshold case, background exposure is an independent contributor that accounts for as much as 70 percent of the total. In the threshold case, background exposure exacerbates the effects of spousal exposure, but the risk could be likely eliminated for any given individual by avoiding spousal exposure alone.

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[79] In 1985, 4550 female non-smokers died of lung cancer from all causes (EPA Report, Table 6-2, p.188). The populations of the various groups of non-smokers are given in Table 6-3 of the EPA report,p.192.

[80] According to the data in Table 3, p.1754 of the Fontham, et.al.paper, 61 percent of the female non-smokers are exposed to spousal cigarette smoke.

The number of lung cancer deaths in the no-threshold case attributable to background ETS is highly dependent on the value of Z -- the ratio of total exposure to background exposure only -- chosen. The EPA calculation used a value of Z = 1.75. As a result, it came up with an estimate of lung cancer deaths -- about 3300 -- somewhat greater than using the Fontham data even though EPA used a relative risk of 1.19 compared to 1.29 for the calculations presented above. The EPA results showed about 71 percent of the lung cancer deaths to be due to background ETS, either by enhancing the effect of spousal ETS or by acting directly on non-smokers unexposed to spousal ETS.

The effect of changing Z can also be seen by re-calculating the numbers in table 1 for a different value of Z. For example, in illustration I above, if Z is doubled to 5.2, the number of lung cancer deaths drops from 2795 to 1820 and the percentage due to background ETS drops from 55 percent to 29 percent. Furthermore, over one half of the deaths attributable to background ETS come from those individuals unexposed to spousal ETS meaning that the effect of background ETS on enhancing spousal ETS drops in relative terms.

There are other concerns about this method of determining the contribution of background ETS. One source of uncertainty is the possible variation of background exposure over time. Such variation is very likely. Whereas spousal ETS exposure is likely to be rather constant over time to the degree that the spouse continues to smoke, background ETS for a given individual could vary substantially. Changing jobs or job locations, variations in social settings, and many other changes in a person's life could substantially change the amount of background ETS to which a person is exposed. Cotinine measurements taken at one time may not represent a true picture of the exposure ratios. If the sample population selected for cotinine measurements represents a variety of background exposure conditions, however, such a problem may not be serious.

It is also plausible that background ETS, and, therefore, cotinine levels of non-smokers exposed only to background ETS, are lower today than 20 or 30 years ago. The Z values predicted from today's measurements are likely to be higher than an average Z over the lifetime of the background exposure and, therefore, would understate the effect of such exposure. At the same time, this downward trend in background ETS may well continue. Formal and informal bans on smoking in public areas mean that fewer and fewer non-smokers are exposed to much ETS if at all. In a survey of workplace facilities by the International Facility Management Association, it was found that 71 percent of the facilities in the survey do not allow smoking in any part of the building compared to 42 percent in 1991.[81] Thus any estimates based on current values of Z probably overstate any future ETS risk.

In the threshold case, the value of Z does not affect the total number of deaths but the share that would be avoided if background disappeared; the higher the value of Z, the smaller the share.

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[81] News Release, International Facility Management Association, Houston,

Finally, it is possible that very few or even no deaths can be attributed to ETS. For the Fontham data used here, the lower bound of the 95 percent confidence interval gives a small number of lung cancer deaths resulting from ETS, less than 500. In a study by Brownson an overall risk value of 1.0 (zero excess risk) was found.[82] That study did find a relative risk of 1.30 above 40 pack-years which was statistically significant at the 95 percent level. Below 40 pack-years, however, it found relative risk values below one, although the results were not statistically significant at the 95 percent level. Calculating lung cancer deaths based on the average risk for the entire exposed population in the same manner as EPA would yield zero deaths using the Brownson data. If a threshold assumption is made, however, a positive number of lung cancer deaths would result.[83] These deaths would be concentrated among the 26 percent of the exposed population receiving the most exposure. Using the same approach as in the Fontham study, such a threshold calculation would yield about 530 deaths. It is also important to point out that the statistical power of the Brownson study is not sufficient to identify a threshold.[84]

RISK COMPARISON

To put estimates of possible lung cancer deaths from ETS in context, it is useful to compare them to other risks resulting in premature deaths. Such a comparison, however, is very imprecise. First, there is a high degree of uncertainty in the estimates of deaths from many causes, particularly for those causes that produce low numbers of deaths. It is not always possible to attribute a death to a particular cause if there are several possible. This problem is evident from the discussions in the previous chapter about ETS and lung cancer. Next, in trying to determine annual risk -- deaths per million, estimates of the population at risk are difficult as is clear from the calculations presented above about possible ETS lung cancer deaths. As a result of these and other uncertainties, some annual risk estimates can be uncertain by factors of 10 or more.[85] Nevertheless, a comparison can still be illuminating as long as these caveats are recognized.

Table 10 (next page) presents comparisons of deaths and death rates due to various causes or various catagories with ETS exposure deaths determined from the Fontham data (with the range representing the 95 percent confidence

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[82] Brownson, et.al., p.1528.

[83] The reason for this apparent contradiction is that a strict application of the method for calculating lung cancer deaths from ETS would yield "negative' deaths from the values of relative risk below 40 pack-years in exposure. In other words, the data would imply that exposure at these lower levels would actually reduce a persons chances of getting lung cancer. While there is no definitive proof that such a result is impossible, it appears very unlikely given the constituents of ETS. Therefore, the most prudent inference from the data is that no excess lung cancer deaths are indicated for these exposure levels.

[84] See footnote 4.

[85] Wilson, R. and Crouch, E.A.C., *Science*, Vol. 268, April 17, 1987, p.268.

interval) and the Brownson study, using the no-threshold assumption. The data in the table are for the U.S. and are from the 1980s time period. The left-hand side of the table gives total deaths from a representative number of causes.[86] The upper end of the calculated range of lung cancer deaths from ETS, is one

Table 10 -- Selected Risk Comparisons

Annual Deaths		Annual Risk Rate (deaths per million exposed)	
Cause	**Deaths**	**Cause**	**Rate**
All Cancers	480,000	Smoking (one pack per day)	3600
Smoking (one pack per day)	150,000	All Cancers	2800
Alcohol	100,000	Automobile	200
Automobiles	50,000	Air Pollution (eastern U.S.)	200
Handguns	17,000	Home Accidents	110
Surgery	2,800	Homicide	100
X-rays	2,300	Drowning	36
Bicycles	1,000	Fires	13
Home Appliance Accidents	200	Electrocution	5
Commercial Aviation	130	One commercial airline trip	0.7
Lightening	70	Lightening	0.5
Skiing	18	ETS-Lung Cancer (Fontham, et.al.,background only)	4 to 30
Vaccinations	10	ETS-Lung Cancer (Fontham, et.al.,spousal exposure)	10 to 135
ETS-Lung Cancer(Fontham,et.al.,data)	470 to 5500	ETS-Lung Cancer (Brownson, et.al.)	0
ETS-Lung Cancer(Brownson,et.al.,data)	0		

to two orders of magnitude below the number resulting from all types of cancer, lung cancer from smoking, and auto accidents. Of course, these catagories are not all mutually exclusive. For example, all types of cancer would include lung cancer from smoking and any ETS lung cancer deaths.[87] The Brownson study, which measures no average risk, and whose confidence intervals extend into the negative risk range, implies negligible or no risk.

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[86] Glickman, T.S. and Gough, M., eds., *Readings in Risk*, Resources for the Future, Washington, D.C., 1990, p. 69.

[87] The mean value of ETS lung cancer deaths calculated from the Fontham data would amount to about 0.6 percent of all lung cancer deaths.

The second half of the table makes comparisons with a selected number of other annual risk rates (in deaths per million exposed to that risk) using the mean risk values.[88] Based on the Fontham study, the risk rate for those exposed to spousal smoke falls between rates from causes such as drowning, but below home accidents and homicide, and far below major causes. The risk for those not exposed to spousal smoke is much smaller, and is in the neighborhood of risks from causes such as fires. The average risk implied by the Brownson study, for either group, is negligible or zero.

Another way of expressing this risk is to compare it with the chance of dying in a given year, or in a lifetime, using some rough numbers. To take a major risk that is similar in nature, the chance of dying from any type of cancer in any one year is about 1/3 of one percent; assuming a life span of 70 years and an equal chance of dying in each year, there is a 20 percent lifetime chance of dying from cancer. Using the Fontham data, there is a 7/1000 of one percent chance of a person exposed to both background and spousal smoke dying from ETS in a given year, or about a 2/10 of a percent chance of dying in a lifetime.[89] For a person exposed only to background ETS, the annual risk is about 2/1000 of one percent and the lifetime risk less than one tenth of one percent. By comparison, auto accidents account for a lifetime risk about 1.5 percent and homicide about 1 percent.

Actually the relative risk is even smaller, especially when compared to causes such as accidents. Lung cancer is a disease of old age; the later in age it occurs the more likely death will occur from some other cause first. Moreover, the loss of years of life will be smaller for a lung cancer death than for accidents and diseases that tend to affect much younger individuals and cause a much greater period of loss of life.

The causes of death also differ in other ways than the age at which they occur. For example there are clear benefits associated with some of the risks such as automobile use. Furthermore, the degree to which they can be avoided differs with the causes as well as the way the risks are distributed among the population. For example, certain jobs are more subject to some kinds of risk, such as indoor air pollution, than others. (Of course, all causes of death added up will be 100 percent).

The threshold models, not shown in the table, would reduce the aggregate ETS in the left-hand side for Fontham, while resulting in a positive estimate for Brownson. In neither case would risk appear for those exposed only to background.

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[88] Wilson, R. and Crouch, E.A.C., p. 268; U.S. Office of Management and Budget, *Budget of the United States Government;Fiscal Year 1992, Part Two,* Washington, DC, 1991, Part Two-368.

[89] Since the reference population is confined to those 35 years old and above, the annual risk is multiplied by 35 rather than 70 to obtain lifetime risk.

OCCUPATIONAL ETS LUNG CANCER RISK

The EPA made no attempt to assess the lung cancer risk from occupational (i.e., workplace) exposure to ETS, arguing there were too few workplace ETS studies to conduct a meta-analysis, and that it is difficult to obtain dependable assessments of workplace ETS exposure. Recall of past workplace exposure is probably not as reliable as for spousal smoking, especially by surrogate respondents. Workplace ETS exposure is less stable than exposure in the home. Over time, people change jobs and offices, their co-workers change, and they may be exposed to various hazardous chemicals that pose a lung cancer risk. Workers may not know that they have been exposed to ETS if it is circulated through the ventilation system, especially if the smell is masked by that of other chemicals.

However, the Occupational Safety and Health Administration (OSHA) did perform an ETS risk assessment as part of its proposed rule to set standards regulating indoor air quality in all indoor work sites.[90] Under the proposal, smoking would only be permitted in separately enclosed, designated smoking rooms that are ventilated directly to the outside. OSHA received a record number of more than 105,000 responses during the public comment period and conducted six months of public hearings on the proposed rule. The docket will remain open until the beginning of 1996 for interested parties who participated in the hearings to submit post-hearing comments.

The public hearings focused largely on the proposed rule's smoking restrictions, which represent only one component of what is a fairly comprehensive indoor air quality regulation. Many independent researchers and other Federal agencies support OSHA's findings and have provided new data to incorporate in revisions to the proposed rule. Tobacco industry researchers and consultants have also submitted a large number of documents criticizing OSHA's ETS risk analysis including new data and analysis. The following comments are made with the clear understanding that OSHA has yet to release a final rule, and that it may choose to make substantial revisions to its proposal before releasing it in final form.

OSHA estimated that the proposed smoking restrictions would prevent 0.4 to 1.0 lung cancer death per 1000 workers exposed to ETS over a 45-year working lifetime. Assuming there are 74 million nonsmokers in the workforce, this is equivalent to avoiding between 144 and 722 lung cancer deaths each year.[91] The agency estimated that the annual cost of compliance with the rule's smoking restrictions would range from zero to $68 million, depending on

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[90] U.S. Dept. of Labor, Occupational Safety and Health Administration. Indoor Air Quality. Notice of proposed rulemaking; notice of informal public hearing. Federal Register, v. 59, no. 65, April 5, 1994. p. 15968.

[91] OSHA also estimated that the proposed rule would prevent between 2,094 and 13,001 heart disease deaths per year. The reader is referred to appendix A for a brief discussion of the heart disease risk of ETS exposure.

whether establishments ban smoking altogether or permit smoking in designated areas. This represents less than one percent of the total estimated cost of the proposed regulation.

OSHA's claim that ETS causes lung cancer is based on its own review of the spousal (i.e. residential) studies that formed the basis of EPA's risk assessment. It argued that the risk estimates calculated from the residential studies are directly relevant to workplace ETS exposure because the risk is determined by the amount of exposure, and not the environment in which that exposure occurs. OSHA claimed, therefore, that in the absence of specific occupational studies, use of residential risk estimates is justified in determining the occupational risk.

If one accepts that there is a causal link between residential ETS exposure and lung cancer, then OSHA's approach is at least partially valid. Further, if occupational ETS exposure levels are similar to those in residential settings where excess risk was measured, then OSHA's estimate of occupational lung cancer risk using residential risk estimates from ETS have merit.

ESTIMATES OF OCCUPATIONAL ETS LUNG CANCER RISK

OSHA provided few details of its review of the ETS residential studies, which concluded that sources of bias and confounding cannot account for the reported ETS-lung cancer risk elevations. Each study was evaluated to determine whether it demonstrated an association between ETS exposure and lung cancer. Fourteen of the studies were characterized as "positive" because, according to OSHA, "they met standard epidemiologic and statistical criteria to support causation."[92] The remaining 17 studies were judged to be either "equivocal positive" or "equivocal." OSHA did not provide any information on the specific criteria by which each study was evaluated. Of the 14 studies that were characterized as positive, only four actually reported a statistically significant increase in lung cancer risk, and only one of these was well-conducted, according to EPA.[93]

It is possible that any observed elevation in occupational risk is due to confounding or misclassification bias.[94] Whereas the evidence that confounding can explain the ETS risk measurements in residential settings is fairly weak, it

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[92] OSHA, 1994. p. 15993.

[93] The four studies characterized as positive by OSHA that reported a statistically significant increase in lung cancer risk were Geng (1988), Trichopoulos (1981), Lam (1987), and Kalandidi (1990). In its 1992 ETS risk assessment, EPA determined that Kalandidi was a well-conducted study, but found the others to be less useful primarily because of concerns about potential confounding.

[94] Smoker misclassification bias is unlikely to be a significant factor in workplace studies because, unlike residential studies, workplace studies are not subject to spousal concordance (i.e., the tendency for smokers to marry smokers).

may be important in the workplace because of the presence of hazardous chemicals. Smoking prevalence, and therefore the potential for workplace ETS exposure, is likely to be greater in hazardous workplaces because they tend to employ blue-collar workers, who smoke more on average than the general population. Indeed, a 1983 study found that over 30 percent of never smokers exposed to ETS were also exposed to hazardous substances at work.[95] Further, the authors found that the exposure to such substances increased, although mildly, as exposure to ETS increased.

OSHA concluded that the ETS lung cancer risk ranges from 1.20 to 1.50. It did not provide any explanation of how it arrived at this estimate, which was presumably based on its assessment of the 14 positive studies,[96] nor did it indicate what this risk is relative to. One assumes that it is the excess risk of lung cancer among non-smoking women exposed to spousal smoke relative to non-smoking women with non-smoking spouses.

Although there are no specific occupational ETS studies, 13 of the residential studies also collected data on workplace exposure and reported occupational lung cancer relative risks. In most cases, the exposed group consisted of persons who reported ETS exposure at work, and the comparison group was persons not exposed at work. It is not possible to analyze dose-response because most of the studies did not stratify risk by workplace exposure level. Moreover, nearly all the studies are potentially confounded by spousal exposure, further complicating analysis and interpretation.

OSHA decided to base its risk assessment on Fontham's occupational ETS-lung cancer risk estimate of 1.34 and not use the other studies. The Fontham study was chosen because it was a large, well-controlled, population-based study the results of which could be generalized to the entire U.S. population. The Brownson study shared many of the strengths of Fontham's study, though Brownson did not report numerical results for workplace ETS exposure. Using the Brownson data, Butler calculated that those with workplace ETS exposure had a slightly reduced risk of lung cancer that was not statistically significant (relative risk = 0.90; 95 percent CI 0.70, 1.15).[97]

The discrepancy between the Fontham and Brownson workplace risk estimates may be due to the substantial difference in the number of surrogates used in the two studies. Two-thirds of the case interviews in the Brownson

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[95] Friedman, G.D. et.al. Prevalence and correlates of passive smoking. *Am. J. Public Health*, v. 73, no. 4, 1983. p.404.

[96] The 14 positive studies reported relative risk estimates ranging from 1.00 to 2.40, which corresponds to a zero to 140 percent increase in lung cancer risk. Relying heavily on positive studies and giving little or no weight to the other, so-called equivocal, studies would clearly bias the outcome because the equivocal studies tend to report little or no risk elevation.

[97] Butler, W.J. Workplace Exposure to ETS and Lung Cancer: A More Detailed Presentation of the Data from a Negative Study, Brownson et al., (1992). Submitted to OSHA Docket H-122, August 1994.

study were conducted using surrogates, compared to a little over one-third in the Fontham study.[98] Surrogates may not provide very useful information about ETS exposure in the workplace. In view of the Brownson study's reliance on surrogate interview data, the Fontham study would appear to provide more reliable data on workplace ETS exposure. (The Brownson and Fontham studies also differed with respect to risk from exposure to spousal smoking, so it is not clear that poorer data are responsible for these differences.)

Levois and Layard performed a meta-analysis using all 13 occupational risk estimates and found no association between workplace ETS exposure and lung cancer.[99] The overall relative risk was 1.00, with a 95 percent confidence interval of 0.92 to 1.09. In a separate meta-analysis using only the 8 U.S. studies, the relative risk dropped slightly to 0.97, with a 95 percent confidence interval of 0.89 to 1.07. Therefore, had OSHA performed a meta-analysis, it seems likely that it would have found no increased lung cancer risk from occupational ETS exposure.

Although the Fontham study may have the most dependable workplace data, OSHA has been criticized for ignoring the other workplace studies and not performing a meta-analysis, as did EPA. An alternative approach would be to use the estimates of risk from spousal exposure. Workplace risk could then be estimated by comparing time-activity and exposure patterns in residential and occupational settings. The outcome would, however, depend largely on the choice of a no-threshold vs. threshold model, as discussed in the previous section.

OCCUPATIONAL ETS EXPOSURE

OSHA estimated that between 18.8 and 48.7 percent of nonsmoking workers are potentially exposed to ETS at their worksite. The higher number was taken from a study by Cummings and the lower number was an estimate from the 1991 National Health Interview Survey (NHIS).[100] The Cummings study got all its subjects from a cancer screening clinic in Buffalo, New York. Clinic attendees were invited to participate in a study on ETS. Those that agreed to participate were asked "whether they had been exposed indoors, not in a car, to smoke from an individual who was smoking" in the last four days. Additional questions were asked regarding specifics of exposure. The NHIS survey assessed workplace exposure by asking participants: "During the past two

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[98] In the Brownson study, 402 (65 percent) of the 618 case interviews were with surrogates, compared to 241 (37 percent) of the 653 case interviews in the Fontham study.

[99] Levois, M.E. and Layard, M.W. Inconsistency between workplace and spousal studies of environmental tobacco smoke and lung cancer. *Regulatory Toxicol. and Pharmacol.*, v. 19, 1994. p. 309.

[100] i) Cummings, K.M. et al. Measurement of current exposure to environmental tobacco smoke. *Arch. Environ. Health*, v. 45, 1990. p. 74. ii) U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey, 1991.

weeks, has anyone smoked in your *immediate* work area?" (Emphasis in the original.)

OSHA argued that the NHIS figure might be an underestimate "because it is based solely on self-reported information and the question was not very specific in defining immediate work area."[101] It should be noted that the Cummings figure was also based on self-reported information. Participants in the 1992 NHIS survey were asked the same question about workplace ETS exposure and their response was very similar to that of the previous year. The 1991 and 1992 NHIS survey estimates of the prevalence of workplace ETS exposure among nonsmokers were 18.7 percent and 20.0 percent, respectively. The similarity between these two estimates suggests that the NHIS survey participants understood what is meant by the phrase "immediate work area."

The advantage of using the NHIS survey is that it is a very large, representative sample of the U.S. population. Indeed, OSHA used it to estimate the percentage of nonsmoking workers in the U.S. that would be covered by its proposed regulation. The Cummings study may be far less representative because of the self-selected nature of the recruited subjects, and the way they were invited to participate (i.e., by informing them it was an ETS study).

Studies using stationary air samplers and personal monitors that were described in an earlier section of this report indicated that offices with smoking occupancy have average nicotine concentrations that are similar to those in smoker-occupied residences. OSHA reanalyzed data from the California Activity Pattern (CAP) Survey and concluded that the "study showed that the most powerful predictor of potential exposure to ETS was being employed.... Further data from this study show that the workplace is the location with the highest reported exposure to ETS in enclosed environments, and such exposure is on average nearly three times more prevalent at work than at home."[102]

Critics of OSHA claim that the CAP survey only yielded estimates of *potential* exposure that do not support OSHA's conclusions. Specifically, the CAP survey asked subjects to record "simply whether there were any smokers present during the activity, and these smokers could have been present for the entire activity or part of it." Such data, by design, address only the potential duration of exposure and overestimate actual ETS exposure, a point made by the study's authors.

Studies that measured cotinine levels in nonsmokers suggest that residential ETS exposure may be more important than workplace exposure. An international study conducted by the International Agency for Research on Cancer found that average workplace ETS exposure is only about one-third of

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[101] OSHA, 1994. p. 15995.

[102] OSHA, 1994. p. 15989.

average residential spousal exposure.[103] Cotinine levels in the Cummings study also indicated that workplace exposure accounted for a relatively small fraction of total ETS exposure. Cummings found that workplace ETS exposure is associated with a 14 percent higher average urinary cotinine level among subjects with household ETS exposure (12.8 ng/ml vs. 11.0 ng/ml). Surprisingly, among subjects without household ETS exposure, workplace exposure was associated with a nine percent *reduction* in the average cotinine level (7.5 ng/ml vs. 8.7 ng/ml).

Cummings indicated that these data may be misleading because many subjects took time off work to attend the clinic. Cotinine levels might therefore be more influenced by home and public location exposures than by work. As cotinine only provides a measure of ETS exposure over the previous two days, it would be useful to document the whereabouts of each sudy participant during that period.

Finally, Butler provided to OSHA a preliminary analysis of cotinine data collected as part of the National Health and Nutrition Examination Survey III (NHANES III), which was conducted by the National Center for Health Statistics (NCHS) between 1988 and 1991.[104] According to this analysis, the contribution of household ETS sources exceeded that of workplace sources by a factor of 5.6 for married male and female workers combined.

This analysis was performed on a "provisional" NHANES III dataset provided by the NCHS to OSHA. A final copy of the data is expected to be submitted to OSHA in the near future. Because of its size and scope, the NHANES III study may provide OSHA with an opportunity to examine the distribution and correlates of cotinine levels in a large and representative sample of the U.S. population.

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[103] Riboli, E. et al. Exposure of nonsmoking women to environmental tobacco smoke: A 10-country collaborative study. *Cancer Causes Control* v. 1, 1990. p. 243.

[104] Butler, W.J. Serum Cotinine Levels and Self-Reported Household and Workplace Exposure to ETS Among Non-Smoking Married U.S. Workers: The NHANES III Study. Submitted to OSHA Docket H-122, September 1995.

APPENDIX A — PASSIVE SMOKING HEART DISEASE RISK AND RESPIRATORY DISEASE RISK IN CHILDREN

While much of the focus of the passive smoking debate has been on lung cancer risks, there has also been some discussion of other potential effects of ETS, notably heart disease in adults and respiratory illness in children. A full analysis of these issues is beyond the scope of this paper, although the insights gained about lung cancer studies can be relatively easily applied in a general way to the heart disease studies. The issue of childhood respiratory disease has a larger scope, and the discussion here will be limited to summarizing in a general way the findings to date and the issues of controversy. It is perhaps also important to note that the heart disease issue has more immediate importance in the formulation of Federal regulatory policies, since exposure of young children is largely in the home. Heart disease risk has, in fact, been included in initial risk estimates prepared by OSHA in its preliminary rulemaking.

HEART DISEASE AND ETS

Extensive research has shown that smoking is a significant risk factor for heart disease. Nicotine and carbon monoxide are both known to have an adverse effect on cardiovascular performance.[105] Nicotine releases adrenaline, which increases blood pressure and heart rate. Research also indicates that it may increase the tendency of blood platelets to aggregate, thereby promoting clotting and increasing the likelihood of a heart attack. Carbon monoxide binds avidly to hemoglobin and reduces blood oxygen transport. Therefore, the heart rate for a given level of activity must increase to maintain the same oxygen supply.

According to the Public Health Service, the overall relative risk of heart disease among ever (i.e., current and former) smokers compared to never smokers is estimated at about 1.7.[106] As is the case with lung cancer, the chemical similarities between mainstream and sidestream smoke and the association of active smoking with heart disease are reasons for a possible relationship between ETS and heart disease, which should be tested using statistical studies. Statistical studies of ETS and heart disease, which also typically use marriage to a smoker as a measure of exposure, are, however, more limited in quality and quantity than the studies of ETS lung cancer. They are also subject to the same types of potential problems as passive smoking lung cancer studies.

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[105] U.S. Dept. of Health and Human Services, 1983.

[106] U.S. Dept. of Health and Human Service. *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General.* U.S. DHHS, Public Health Service, Office of the Assistant Secretary of Health, Washington, DC, 1983. DHHS Pub. No. (PHS) 84-50204.

The Surgeon General's 1986 report on passive smoking discussed heart disease but reached no specific position and the EPA study did not address this issue, although heart disease was considered by OSHA in its notice of proposed rulemaking -- and actually accounted for more of the risk than lung cancer.

In August 1992, the American Heart Association (AHA) concluded that ETS is a major preventable cause of cardiovascular disease and death.[107] The AHA statement was based on a 1991 report by Glantz and Parmley, which reviewed the biochemical and physiological evidence of a link between ETS and heart disease, and a risk assessment published by Steenland.[108] Glantz and Parmley have also published an update, and their reviews include some laboratory evidence of physiological changes in animals and human beings (although this does not establish an effect on diseases and deaths).[109] Two laboratories have demonstrated that acute exposure in humans affects measures of platelet function in the direction of increased tendency toward thrombosis, although in one of the studies the exposure level was extremely high. Similar assays of platelet function in active smokers have not produced consistent results. Several studies of long-term ETS exposure in animals indicated a buildup of arterial plaques, and there is limited evidence of similar effects in humans. The Steenland paper reviewed the available epidemiologic data and concluded that ETS causes an estimated 35,000 to 40,000 heart disease deaths per year in the United States.

The view of the American Heart Association has been disputed by the industry and questioned by some researchers; indeed, some of those who have produced estimates clearly have reservations about the magnitude of the risk estimated. The industry has also criticized OSHA, not only for its assessment of the heart disease risk, but also for its reliance on one residential study to produce risk estimates for the workplace.[110]

Last year, Wells published an updated analysis of the 12 available epidemiologic studies of passive smoking and heart disease.[111] He estimated that passive smoking causes 62,000 heart disease deaths each year. Wells adopted the same procedures that he and his colleagues used in the EPA report to compute the number of passive smoking lung cancer deaths. The 12 epi

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[107] Taylor, A.E. et al. *Circulation*, vol. 86, 1992. p. 1-4.

[108] (i) Glantz, S.A. and W.W. Parmley., *Circulation*, vol. 83, 1991. p. 1-12. (ii) Steenland, K. *J.Am. Med. Assoc.*, vol. 267, 1992. p. 94-99.

[109] S. A. Glantz and W.W. Parmley., *J. Am. Med. Assoc.* vol. 273, 1995, pp. 1047-1053.

[110] For two papers that are direct critiques of the position of the AHA, see Gio Batta Gori, *Regul. Tox. Pharmac.*, vol. 21, p. 281-295.; W. J. Butler, Epidemiologic Studies of Heart Disease and Spousal Smoking Status: Limitations of the Study by Helsing, et al. (1988) and Review of Uncontrolled Confounders. Comments to Docket Office, Docket No,. H-122, U.S. Department of Labor, August 1994.

[111] Wells, J.A., *J. Am. College of Cardiology*, vol. 24, no. 2, 1994. p. 546-554.

studies were assigned a quality tier ranking of 1 to 4 and weighted according to study size. In addition, each relative risk was corrected for confounding and adjusted for smoker misclassification bias. Wells calculated an overall passive smoking relative risk (RR) of 1.22. Whereas the EPA estimate of passive smoking lung cancer deaths used a value of Z = 1.75, Wells chose a higher value of Z = 2.6, based on Fontham's study, in order to estimate the number of ETS-related heart disease deaths. The heart disease epi studies include several estimates of relative risk among never-smoking males. Wells reasoned that men are exposed to more background ETS than women and calculated a value of Z = 2.1 for the male studies.

The estimate of 62,000 heart disease deaths attributable to passive smoking far exceeds EPA's estimate of 3,000 ETS-related lung cancer deaths, even though the number of deaths attributed to active smoking is similar in magnitude. Heart disease is the leading cause of death in the United States. Almost half a million people die from heart disease each year, of which an estimated 180,000 deaths are attributed, by the public health service to smoking. Lung cancer is the cause of approximately 150,000 deaths annually, 80 percent of which (120,000) are attributed to smoking. Thus the risk to nonsmokers of heart disease (from any cause) is much larger than the risk of lung cancer. Therefore, even though the odds ratios for heart disease due to ETS in the Wells study are similar to those used by the EPA for lung cancer, the absolute risk implied is much higher (the heart disease risk is a percentage of a much larger number). Thus, whereas EPA's estimate of the ETS-related lung cancer risk (RR_s = 1.19) among never-smoking women is a small fraction (2 percent) of the lung cancer risk for ever-smoking women (RR = 11), Wells' estimate of the ETS-related heart disease risk is *almost one-third* of the risk among ever smokers.

Because of these relationships, some investigators have questioned the biological plausibility of the passive smoking heart disease risk estimates.[112] Half of the studies reported relative risks greater than 1.7, the estimated heart disease risk ratio among ever smokers. Moreover, the passive smoking to active smoking risk ratio — approximately one-third — is much greater than would be predicted from an analysis of nicotine levels in passive and active smokers. Studies of urinary cotinine levels indicate that passive smokers receive less than one percent of the nicotine exposure of active smokers. Carbon monoxide exposure from passive smoking is also likely to be a small fraction of the amount to which active smokers are exposed.

The discrepancy between the heart disease risk indicated in the ETS epi studies and the relatively small amounts of nicotine and carbon monoxide to which passive smokers are exposed implies (if the estimates are correct) that the body's response to ETS must be significantly greater than one would predict from a linear dose-response relationship. Currently, the data to support such

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[112] In addition to sources cited in the previous note, see Huber, G.L. et.al., *Consumers' Research*, April 1992. p. 18. and Samet, J.M., Environmental Tobacco Smoke, *Environmental Toxicants: Human Exposure and Their Health Effects*, Lippman, Morton, ed., Van Norstrand Reinhold, New York, 1992.

a relationship are limited. Some evidence has been presented to suggest that non-smokers are more sensitive to additional exposures than smokers because smokers are chronically exposed, and even that there may be a ceiling in responsiveness to smoke at low levels. Of course, it is not clear how these observations are consistent with dose response effects in active smokers or how they might be relevant to chronic ETS exposure that appears in spousal studies.

An alternative explanation is that the current epidemiologic studies are not capable of measuring heart disease risk. As noted previously, the lung cancer studies are not in agreement, and there are uncertainties with each ETS study; various misclassification types and confounders. Smoker misclassification is much less important for heart disease than for lung cancer, because the active smoking risk for heart disease is so much smaller than for lung cancer. Confounding, however, could be a much greater problem both because there are so may other factors that are significant contributors to heart disease risk and because most of the studies inadequately control for these effects.

Smokers tend to have lifestyles that put them at greater risk for heart disease. In general, smokers are less health conscious than nonsmokers. They tend to drink more alcohol, eat less healthy diets, exercise less, and have a lower socioeconomic status. The degree to which non-smoking spouses of smokers share their partner's unhealthy lifestyle has not been studied extensively, but it is likely that some of the risks are shared.

Eighteen potential confounders for heart disease were identified in the epi studies including blood pressure, blood cholesterol, body weight, socioeconomic status, personal history of heart disease, exercise, diabetes, and diet. These factors are not all independent of one another, but only four of the 12 epi studies controlled for at least six of them. Over half of the cases in the combined analysis came from one study, which failed to control for any of the potential confounders listed above.[113]

Further indications that these results may be too large are found in the publication of two large new studies that found no risk of heart disease from passive smoking.[114] One of these studies also suggested that there is evidence of publication bias.[115]

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[113] Sandler, D.P. et al., *Am. J. Public Health*, vol. 79, 1989. p. 163-167.

[114] M. W. Layard, *Regul. Toxicol. and Pharmacol.*, vol. 21, pp. 178-180;
M. E. LeVois and M. W., *Regul. Toxicol. and Pharmacol.*, Vol. 21, pp. 181-188.

[115] LeVois and Layard report that small studies tend, as a group, to report larger risk ratios than large studies, evidence that would be consistent with a tendency to publish small studies with statistically significant results, but not ones with null results. Again, this publication bias is not necessarily a deliberate one, but simply reflects the fact that we learn very little from a small study that does not find an effect, because the power to detect an effect is small. Researchers may be less likely to report or submit studies with null results, and editors less likely to publish them. The problem arises when an unrepresentative sample of studies are combined in a meta analysis, or when an overall judgment is made about the body of evidence which includes a biased sample.

Because of the potentially very large public health impact of ETS on heart disease, a comprehensive assessment and additional research program should be undertaken.

ETS AND RESPIRATORY DISEASE RISK IN CHILDREN

It is more difficult to assess the literature on respiratory disease risk of ETS on children; indeed, although the EPA reached a variety of conclusions about this issue, there was no overall quantification through a meta-analysis as in the case of lung cancer. These studies are heterogeneous in types of diseases studied, measures of outcomes, and measures of exposure. Nor has there been an extensive critique of this research by the industry, although whether this absence of criticism reflects greater acceptance or because the issue is less closely tied to direct regulatory policies such as workplace restrictions is unclear. Finally, unlike the case of heart disease, it is more difficult to assess these studies by applying insights from examining lung cancer studies.

This summary is confined to describing briefly the conclusions reached by the EPA survey of the literature, summarizing some of the potential problems investigators confront in assessing these effects (most of which are described in the EPA report itself), and briefly discussing the problems of risk assessment for these health outcomes.

The EPA report refers to over 100 studies of effects of ETA on childhood illnesses, covering acute respiratory illnesses; acute and chronic middle ear diseases; cough, phlegm, and wheezing; asthma; and sudden infant death syndrome. Some of these studies are covered in earlier assessments such as those of the Surgeon General's 1986 report; others are discussed in the EPA report.

The theory supporting these outcomes is not necessarily that ETS can cause most of these diseases, which may be caused, for example, by infectious agents, but that exposure to ETS causes physical symptoms that make children more vulnerable to diseases.

The EPA concluded that studies of acute respiratory illnesses (approximately 20) provided strong evidence of an effect, but that evidence is less persuasive for older children, and for smoking fathers. They found some evidence for middle ear diseases but acknowledged a variety of problems that precluded more definitive conclusions. They found strong evidence for increased respiratory symptoms (cough, phlegm, and wheezing) in infants and young children. They indicated that ETS exacerbates asthma in children that already have the disease, but that evidence regarding inducing of asthma is not conclusive and would probably require a high level of exposure in any case. For a variety of reasons, they were unable to determine the effect of ETS on SIDS. The EPA report concludes that there is a causal relationship between ETS and reductions in lung function.

There is an extensive discussion in the EPA report of potential problems associated with these studies, as well as measures taken to deal with these problems. The following brief discussion summarizes some of the potential problems with bias and confounding, most of which were addressed directly in the EPA report.

First, the effect of prenatal smoking by the mother cannot be easily disentangled from the effect of ETS after birth; not all studies control for this effect and for those that do, some recall bias may be present (e.g., mothers may indicate that they did not smoke during pregnancy when they did). In some cases, but not all, an effect has been found for fathers. Using the father as a control for prenatal smoking is of limited usefulness, however, because the father is unlikely to be in as close contract with the child as the mother.

Illnesses, including acute illnesses requiring hospitalization, may be greater among lower income individuals or those with less education for a variety of reasons (e.g., lack of access to a doctor resulting in neglect of a minor illness until it develops into a major one, lack of skill and resources in managing a minor illness or engaging in preventive health measures, housing conditions such as crowding that increase exposure to siblings or limit outside play). Many studies did not control for any aspect of socioeconomic status, and most that did use such controls did not use the most general one, income. Absence of controls for this factor would tend to exaggerate the relationships between parental smoking and health problems, at least in U.S. studies, since smoking is associated with lower incomes.

For studies that base their outcomes on reporting by parents, smoking parents may overestimate the incidence of respiratory problems. This effect can occur because adults who have respiratory problems may be more likely to report respiratory problems in their children, and smoking parents are more likely to have respiratory problems. This effect would bias the results upward, and cannot be easily controlled (indeed, controlling for these effects would probably overcorrect and understate ETS effects). A related effect would occur if physicians are more likely to diagnose respiratory problems (e.g. asthma) in children whose parents smoke.

Some studies were retrospective in nature, and thus are subject to recall bias. If parents whose children have been ill tend to recall more smoking than parents whose children were not ill, an upward bias in the estimates would occur.

Some studies had significant refusal rates (unwillingness to participate in the study); in general, a high refusal rate can cause a sample not to be random and can bias the results.

Smoker misclassification, while not a problem with young children, can become an issue in studies that examine older children, since children are likely to conceal their smoking habits from their parents, and usually the parents

answer the questionnaires. Cotinine tests can correct for this effect, but cannot always be administered.

Many of the studies are small, which means that the finding of null results may not be very meaningful, especially if the number of studies is limited. On the other hand, there is also a possibility of publication bias.

Finally, there may be a relationship between smoking and attitudes towards health that transcend socio-economic class; that is, smokers may in general consider health issues less important than non-smokers. There is evidence that smokers engage in a series of unhealthy or risk-taking behaviors that would support such a theory. If these attitudes in turn affect how they manage illnesses in their children, differences in outcomes may be the result of behaviors other than exposure to ETS. This sort of effect is not easy to control for.

To illustrate how these problems relate to assessment of effects, and make it more difficult to assess relationships, consider the case of asthma, an issue that has attracted some attention. There are a limited number of studies that are described in the EPA report. Of the ten studies, two reported no effect, one of which was a very small, direct experiment; another study found no significant effect for girls and an effect for boys only if both parents smoked. One study found only increased emergency room visits but not hospitalizations or reported incidence. One did not directly study asthma episodes, but rather a response to subfreezing air. One study found no effect in the case of better educated mothers or less than 10 cigarettes a day; one found no effect with less than ten cigarettes a day. Out of the 8 studies that found some effects, none controlled for income, and only three for a substitute aspect such as education. At least five studies included teenagers where smoker misclassification could be a problem (although there were apparently attempts to exclude known smokers). Some of the studies required retrospective recall of smoking habits or incidence of symptoms.

One can see why it may be difficult to assess studies that are so diverse in the types of limitations. While most of these studies found some effects, most of the studies also suffered from some limitations arising from study design. Were one to consider the larger body of research on acute respiratory illnesses, a different set of problems might be identified -- for example, misclassification is less likely to be a problem since these studies were largely focused on young children, but confounders such as income level and prenatal smoking might be more serious.

It is also difficult to translate these findings into risk assessments. For example, the EPA report limited its estimates to acute respiratory disorders and asthma, because of the difficulties of quantifying conditions such as coughing and reduced lung function. For asthma, the EPA's base case attributed 7 to 9 percent of new cases -- 8,000 to 26,000 new cases per year -- to ETS, but indicated that estimate is dependent on the conclusion that asthma is a risk factor for induction. This estimate used a threshold model. It also concluded that about 20 percent of asthmatic children (current totals for under 18 are 2

to 5 million) have exacerbated symptoms; this estimate included an extrapolation for background exposure. There was no quantification of how much exacerbation occurred.

In the case of acute respiratory illness, the EPA estimated that 300,000 cases are due to ETS, with 7,500 to 15,000 hospitalizations. These estimates were confined to effects for children under 18 months.

As noted earlier, it is likely that much of the exposure to ETS, especially among young children, may be due to exposures in the home by parents where regulation cannot have an effect, and any government role would probably concentrate on education. While ETS may pose a serious risk to young children in the home, such education programs would probably be most effective by emphasizing all of the risks resulting from parent's behavior that these children face in that environment.

APPENDIX B -- RESIDENTIAL EPIDEMIOLOGICAL STUDIES OF PASSIVE SMOKING AND LUNG CANCER

The study number at the end of the listing, where appropriate, refers to the study number listed in tables 3, 4 and 5. The last name of the lead author in bold at the end of the listing refers to the listing in figure 1. When two studies by the same author appears in figure 1, the first study that appears is indicated by the number one appearing at the end of the author's last name in bold.

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